The Journal of Allergy

VOL. 15 NOVEMBER, 1944 NO. 6

Original Articles

A POLLEN DEHYDRATOR*

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THEORETICAL CONSIDERATIONS

THE proper dehydration of pollen is of great practical importance, for an extract of the pollen is seldom made during the season that pollination occurs; usually, at least six months elapse between the times of harvesting and extraction. During this period, two factors may act to destroy the antigenicity of the pollen, namely enzymes and oxygen. In the absence of water, neither can act, and it is well recognized that pollen may be stored for long periods if properly dried and kept dry.[1] But a search of the literature has failed to reveal what constitutes a dry pollen or to indicate how dry a pollen should be if its antigens are to be preserved. Most dealers in pollen claim their products to be "thoroughly dried" but fail to specify the percentage of moisture remaining in them, the method of drying used, or how long they stood in the moist state before being dried. We have hearsay evidence of the existence of various machines for drying pollen, but we have seen none described. It appears that most dealers dry their pollens by exposing them to air in a thin layer for twenty-four to forty-eight hours. Durham[2] has shown that the moisture content of pollen closely follows the relative humidity of the air surrounding it, which would make it appear that the present methods of drying are rather haphazard and that some uniformly reliable and reasonably rapid method should be devised which would insure adequate drying, irrespective of atmospheric conditions. The purpose of this paper is to describe a machine which will consistently and rapidly dehydrate pollen to such a degree that residual moisture is inappreciable.

A POLLEN DEHYDRATOR

It was felt that the present method of drying pollen in air was good, but that it was too slow and too dependent upon atmospheric condi-

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tions. Our dehydrator is merely a device which holds the pollen in an atmosphere which is constantly maintained at optimum conditions for rapid and complete drying.

The apparatus (Fig. 1) consists of an airtight box with brackets and shelves for holding trays and storage bottles, over which a stream of warm, dry air is circulated. A door on one end permits the manipulation of trays and bottles in a minimum of time. A blower on the top of the box draws air from its interior (the drying chamber), forces it through a tank containing the drying agent (the drying tank), from which it passes over heating coils to enter the bottom of the drying chamber. A thermostat in the latter, adjustable from the outside without opening the door, controls the operation of the heating coils and thus the temperature within the box. Baffles are arranged in the tray brackets which force the air to circulate over the tops of the trays. A sheet of asbestos above the bottom opening disperses the warm, dried air entering the box and prevents the formation of a hot spot on the lower tray. In other words, the machine is so designed that warm, dry air entering at the bottom is forced over the tops of the two trays which contain pollen, then is withdrawn, dried, heated, and again put into circulation.

The balance between the rapidity of circulation of the air and the control of the temperature within the box is rather critical and requires elaboration. The maximum speed at which the air can be circulated is dependent upon the physical characteristics of the pollen. If circulation is too rapid, pollen will be picked up and dispersed throughout the machine with the loss of a large part of it. The air must therefore have a slow, gentle motion. However, if circulation is too slow, heat will not be carried away rapidly enough from the heating coils and will be concentrated in the lower portions of the box, overheating the lower tray.

The greatest resistance to air flow is offered by the drying agent, and the rate of circulation will depend on the length of the column of drying agent and the force of the blower. A rheostat should be used to control the blower speed; however, because of the exigencies of war, a makeshift had to be used in our machines, namely the electric light bulb which appears on the top of the box in Fig. 1.

In adjusting the machine, the only criterion of proper operation is the temperature difference between the top and the bottom trays. It was decided to utilize a temperature of approximately 40° C., for it is known from long experience that this is safe. It is, therefore, necessary to regulate the blower speed, thermostat, and the amount of drying agent until the tray temperatures are at the desired level and approximately the same. This is not difficult, and once the proper blower speed and drying agent column are found, they need no further attention. Under proper operation, we were able to attain a temperature of 39°

C. on the top tray and 41° C. on the bottom. When the air current was too slow, differentials of as much as 15° C. were recorded.

The heating coils are located in the air duct connecting the bottom of the drying tank with the bottom of the drying chamber. They dis-

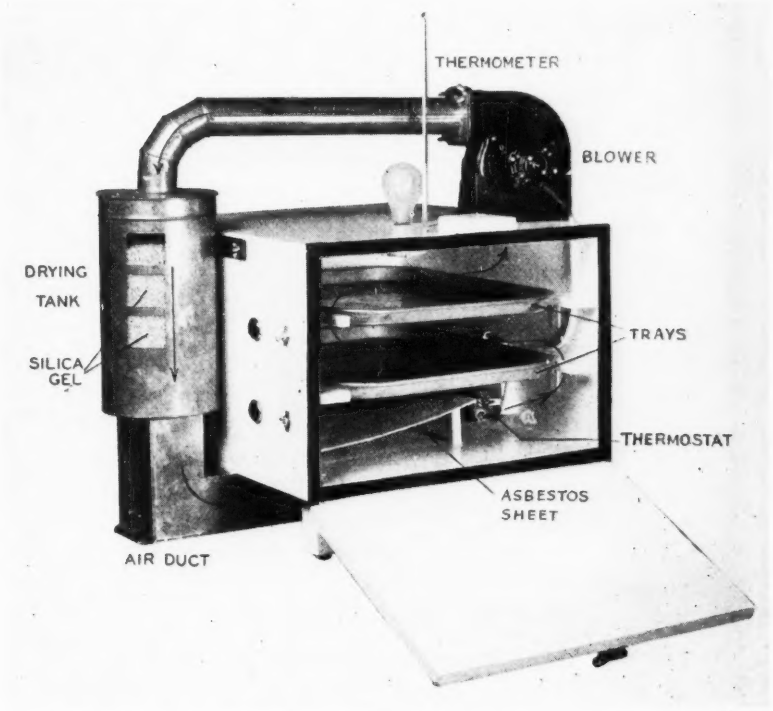

Fig. 1.—Pollen dehydrator. Arrows indicate the course of air flow.

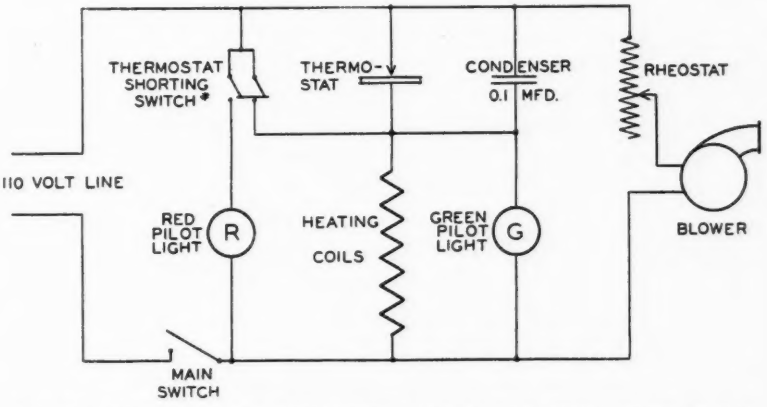

Fig. 2.—Circuit of pollen dehydrator. *Double pole, single throw switch.

sipate 150 watts of heat. A green pilot light on the side of the box is connected in parallel with the heating units so that it shines when they are in operation (Fig. 2). A switch is also provided to short-

circuit the thermostat for quick heating. When the thermostat is short-circuited, a red pilot light is illuminated.

Considerable thought was given to the subject of the drying agent. Sulfuric and phosphoric acids will give the lowest relative humidities to air that it is possible to obtain. However, their great chemical activity and their tendency to creep up the sides of containers renders them impractical for a machine of this kind. Calcium chloride was tried, and, under the conditions of operation, reduced the relative humidity within the drying chamber to 34 per cent. A relatively new drying agent, silica gel, was finally settled upon. This gave a relative humidity of 29 per cent, was cleaner and easier to handle than calcium chloride, and was easily reactivated once its capacity to hold water had been reached.

SILICA GEL

Because this very useful drying agent[3] appears to have been overlooked by biologists, it seems worth while to describe it briefly. Silica gel may be considered a synthetic sand made by the addition of sulfuric acid to sodium silicate under controlled conditions. Its color and texture are similar to that of sand and it is commercially available in sizes of from four to three hundred mesh. That used in our machine was the standard six to sixteen mesh, which is the usual size for drying air. Silica gel is highly porous, and it is this porosity which removes the water from air by adsorbing it in the minute canals with which it is honeycombed. Approximately 50 per cent of the volume of the gel is accounted for by these canals or pores, the diameter of which is about 4 microns. From this it is evident that the surface area inside the pores is tremendous and it has been calculated that 1 Gm. of silica gel contains an internal surface area of approximately 6,000,000 square centimeters.

Silica gel will adsorb up to 40 per cent of its weight in water, but its efficiency decreases as more water is taken on, and, in practice, values from 10 per cent to 20 per cent are used. In the adsorption process, heat is given off at the rate of about 800 calories per gram of water adsorbed. This is of some advantage in our machine, as it lessens the amount of heat which must be added to bring it up to the required temperature.

The gel is available in a very convenient form known as the "Tell Tale" brand. A cobalt salt has been added to this, rendering it a brilliant blue color when dry, which fades to a light pink as water is adsorbed. Thus it can be told at a glance when the gel has reached its capacity of water adsorption and is ready for reactivation. Reactivation is accomplished by heating it to a temperature between 150° C. and 180° C., until the blue returns, which usually takes two to four hours if it is merely placed in an oven and no method of circulating hot air through the gel is utilized.

OPERATION OF POLLEN DEHYDRATOR

Before putting pollen in the machine, the empty trays are placed on the brackets, the door closed, and the switch which starts the operation of the blower and the heating coils is turned on. If the thermostat has been correctly adjusted in advance, it takes about one-half hour on a warm day for the temperature of the top tray to reach the desired 39° C. If the weather is cold, more time is required. Because the thermostat is located in the bottom of the drying chamber not far from the heating coils, the latter may be turned off by the thermostat before the top of the chamber is heated adequately. The thermostat short-circuiting switch may then be used with a considerable saving of time. However, care must be taken that pollen is never placed in the machine when the red pilot light (indicating short-circuit of the thermostat) is on, because there is great danger of overheating with possible destruction of the pollen.

When the desired temperature has been attained and further thermostat adjustments have been made if found necessary, the trays are removed, glazed paper is placed on them, and the pollen is spread out in a thin layer on the paper. The trays, now containing the pollen, are replaced in the machine and the door closed. There will be a slight drop in temperature in the drying chamber due to having opened the door, but when large amounts of pollen (500 to 1,000 grams) are dried at one time, the cooling due to evaporation becomes appreciable and the temperature at the top of the box drops considerably below that of the bottom; a difference of as much as 6 or 7 degrees may be experienced. As drying becomes more complete, and evaporation less rapid, the temperature gradually rises until the original 39° C. is reached, at which point rapid evaporation has ceased. In operation, therefore it is first necessary to run the machine empty until the desired temperature has been attained to be certain that the thermostat is so adjusted that it will not permit overheating of the lower tray with possible destruction of the pollen in it. After the pollen has been placed in the tray, the thermostat should not be adjusted to give more heat no matter how low the top temperature falls.

The top thermometer tells when drying is near completion. When it reaches the reading it had before the pollen was placed in the machine, cooling due to evaporation has become inappreciable. Another two hours should be allowed, however, to be sure that drying is complete and in no case should a run be shorter than five hours.

PERFORMANCE OF POLLEN DEHYDRATOR

The subject of what constitutes a dry pollen will be taken up in a subsequent paper. It will suffice to say at this time that as a comparative method by which to judge the efficiency of the dehydrator, drying of pollen under high vacuum was used. Samples of commercial air-dried pollens, when subjected to high vacuum drying in the cryochem appara-

tus, were found to lose between 5 and 20 per cent of their weights. A good commercial pollen will average between 8 and 10 per cent of water as measured by this method.

As a test run, 500 grams of ragweed pollen, which had already been air dried and which was found to contain 6.4 per cent moisture, was placed in the preheated machine. Such a large amount is about half the capacity of the machine and is more than would be collected in one day by the most ambitious collector. Samples were removed every hour and the residual moisture determined by high vacuum drying. The greatest loss of water was found to take place in the first hour; at the end of five hours, no more water could be extracted by high vacuum.

Numerous runs made by a pollen collector at the time of collection resulted in pollens containing from zero to 2 per cent moisture. Laboratory runs always completely dehydrated the pollen. The reason for the discrepancy is probably that water was absorbed by the pollen while being weighed and handled in humid air.

SUMMARY

1. A machine is described which will dehydrate pollen to virtual completeness in a few hours, compared with an average residual moisture content of 8 to 10 per cent after twenty-four to forty-eight hours of drying in air.

2. The dehydrator is readily portable and easy to operate.

3. It is believed that better keeping qualities will be experienced in pollens rapidly and completely dehydrated.

4. Further work is being done to determine the most effective method of handling pollens which are to be stored.

The assistance of Mr. F. H. Hodgson, botanist, Verona, New Jersey, in making field trials on the machine, and of Professor C. O. Mackey, of the Department of Heat Power Engineering, Cornell University, Ithaca, New York, in giving much useful advice on the construction of the machine, is gratefully acknowledged.

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THE RELATIONSHIP BETWEEN SPONTANEOUS ALLERGIC CONDITIONS AND ASCORBIC ACID: AN EXPERIMENT EMPLOYING SKIN TESTS AND ASCORBIC ACID ON SUBJECTS WITH HAY FEVER*†

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INTRODUCTION

THE question of a possible relationship between ascorbic acid and allergic states was recently revived by Holmes.[1, 2] He stated that 88 per cent of twenty-five patients with hay fever were improved with doses of ascorbic acid as large as 500 mg. per day.

A search through the literature reveals that there has been a great deal of work on the relationship between ascorbic acid and allergic phenomena. In a very thorough article, Walzer[3] gave a critical review of work dealing with ascorbic acid and sensitized guinea pigs. He described the experimental work and told of the conflicting results which have been obtained.

In 1936, Epstein[4] reported the favorable effect of ascorbic acid on patients with asthma. During the next year Heise, Martin, and Schwartz[5] reported that the use of 200 mg. of ascorbic acid intravenously reduced the skin reaction of patients sensitive to tuberculin. Soon after this, Hagiescu, Bazavan, Criscota, and Cioranesco[6] used ascorbic acid for treatment and reported that fifteen of twenty cases of refractory asthma gave good or favorable results. They gave 200 to 300 mg. intravenously during an attack and 100 mg. several times a month when the patients had no symptoms. In the same year, Hunt[7] reported that he found no positive results after treating twenty-five patients with allergy with 50 mg. of ascorbic acid twice a day. Five of the patients were seen during an attack and were given 500 mg. intravenously and 1,200 mg. intramuscularly; however, they were not relieved. Diehl[8] stated that he obtained good results by treating his asthmatics with 300 mg. of ascorbic acid intravenously. Rosenburg[9] treated seven patients for urticaria with ascorbic acid and reported good results. All six had a low initial plasma level of ascorbic acid. In 1939, Wagner[10] stated that he gave ascorbic acid to several patients with newly developed eczema who also had a low plasma level of ascorbic acid. The patients took 150 mg. a day orally and recovered in a short time. In two cases the ascorbic acid was discontinued, and the eczema reappeared. These two persons were again cured with ascorbic acid. At about the same

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†This paper was submitted as a thesis for the degree of Bachelor of Science in Medicine in Duke University.

time (1939), Shaw and Thelander[11] published a rather full discussion of the entire clinical problem. They concluded from clinical experience that ascorbic acid will aid in preventing allergic conditions if given to infants. They give infants 25 mg. a day and believe that this reduced allergic colic. Kennedy[12] gave an oil suspension of adrenalin and ascorbic acid intramuscularly to his asthmatic patients. He seemed to think that added relief was obtained in this manner; however, he concluded that the benefit was due to the longer action of adrenalin when mixed with ascorbic acid. Goldsmith, Ogaard, and Gowe[13] determined the blood plasma level of ascorbic acid in twenty-nine asthmatics and found that it was 0.41 ± 0.051 mg. per 100 c.c. against a level of 0.602 ± 0.049 mg. in forty-three controls; hence, they concluded that asthmatics needed more ascorbic acid. They found that some cases improved with large doses.

During the last year, Hansen-Prüss and Goodman[14] have given large doses of ascorbic acid to over 100 asthmatic patients. They are of the opinion that the patients have not been helped. Dees,[15] who has also treated a number of patients with allergy with ascorbic acid, agrees with this last statement.

It should be pointed out that many of the patients treated for allergic conditions were not proven to be truly allergic. Thus, it is quite possible that some of the reported cures resulting from treatment of presumable allergic conditions were due to psychological factors.

There are many theories as to why ascorbic acid should be useful in treating allergic conditions. Some look upon the reduced sensitivity as being caused by a decrease in the permeability of the capillaries.[5] Others think that epinephrine is made to act longer or more effectively.[7, 12] Hunt pointed out that hypersensitivity to foreign proteins appears after adrenalectomy in dogs. He maintained that hypoplasia of the adrenal glands has been noted in asthmatics at autopsy. Eosinophilia is found in Addison's disease and in allergic conditions. The adrenal gland is rich in ascorbic acid, and epinephrine is the best antiallergic remedy known. Holmes[1, 2] went so far as to say that he bubbled air through a mixture of histamine, water, and ascorbic acid, and has observed that the ascorbic acid was destroyed. Since histamine is released in acute allergic attacks, Holmes concluded from his experiment that ascorbic acid is destroyed in large amounts by patients with allergic diseases and, hence, need more ascorbic acid than the normal person. Holmes, however, did not use a control in his experiment. Since ascorbic acid is so easily oxidized one would expect it to be destroyed in water through which air was bubbled.

Some physicians give ascorbic acid to patients with allergy because they have observed that these patients have a lower ascorbic acid level than normal controls.[13] Shaw[11] takes the stand that lack of ascorbic acid may cause an allergic condition to develop. In a rather full discussion of the problem, he stated that: (1) It has been demonstrated that

guinea pigs low in ascorbic acid are easily sensitized. (2) Animals which synthesize their own ascorbic acid are refractory to sensitization. (3) Ascorbic acid is related to the permeability of tissues. (4) the human infant is likely to have a low supply of ascorbic acid during the first 4 months of life. (5) Allergic states are common in peoples with with a low ascorbic acid diet, as the Chinese of San Francisco and the natives of Scandinavia. (6) In later life, allergies develop after gastro-intestinal disturbances which lead to a low ascorbic acid intake. (7) Man is the only animal which eats cooked food in which much of the ascorbic acid is destroyed. (8) Patients with allergy often have a low ascorbic acid level.

It is obvious from the conflicting views presented that no proof one way or the other has been presented by any worker using ascorbic acid on allergic humans. Little has been offered except impressions. In the following paper, I have attempted to shed some light on the problem by using an objective test which can be measured, namely, the skin test.

EXPERIMENT

The present experiment does not concern the question, whether allergic patients tend to be deficient in ascorbic acid, but rather whether massive doses of the vitamin given orally have an effect upon the skin test in a definite allergic condition, regardless of the deficiency or the adequacy of the vitamin in a subject.

The plasma levels of ascorbic acid as given in Table I were determined by the Mindlin-Butler[16] method in most cases. In thirteen instances, due to difficulty in obtaining blood samples, urine saturation tests were carried out. One thousand milligrams of ascorbic acid were given orally. The bladder was emptied and the urine of the next six hours was collected in a 10 per cent acetic acid solution. This was titrated at once into a standardized solution of sodium, 2,6-*di*chlorophenolindophenol. The data on the saturation tests are not recorded; however, they paralleled the data obtained by the Mindlin-Butler method.

The eight subjects were young adult males who had suffered from periodic attacks of hay fever since childhood. None of the skin tests were made during an active period of hay fever. All were skin sensitive to an extract of short ragweed. The skin tests were made with 0.06 c.c. of 1:1,000 dilution of a standard extract of short ragweed pollen on the forearm about 4 cm. from the antecubital fossa. The lateral diameter of the erythema was always measured by the same person with a centimeter rule fifteen minutes after the antigen was injected.

On the day which the tests were made, the subjects ate a breakfast low in ascorbic acid. The smallest amount of the vitamin given before the second skin test was 1,000 mg. on the first day and 500 mg. on the second and third days. The largest amount given was 1,000 mg. a day for six days. The daily amount of ascorbic acid was divided into three

TABLE I

SUMMARY OF EXPERIMENTAL DATA

SUBJECT AND TEST NUMBER	DATE	PLASMA ASCORBIC ACID (MG. %)	REACTION				DOSAGE
			BEFORE (CM.)		AFTER (CM.)		
H. L. N.							
1	10/26/42	0.5	L5.1				None
2	10/30/42	1.6			R4.0		1,000 mg. per day for 3 days
3	11/ 2/42	1.9			R3.0	L4.0	1,000 mg. per day for 6 days
4	11/25/42	0.3	L4.2	R4.1			None
5	11/27/42	0.5	L4.0	R4.5			None
6	12/ 1/42	0.7	L3.0	R3.5			None
7	12/ 9/42	0.4	L3.8	R2.8			None
8	1/18/43	+	R5.3				None
9	1/26/43	+			R5.5		1,000 mg. per day for 4 days, and 500 mg. per day for 3 days
10	2/11/43	+	R4.1				None
11	2/19/43	+			L3.5		1,000 mg. per day for 4 days, and 500 mg. per day for 3 days
12	10/28/43	+	L5.5				None
13	12/ 1/43	+			R4.2		1,000 mg. per day for for 4 days
14	12/15/43	+			R4.2		1,000 mg. per day for 4 days
15	3/ 9/44	++			L4.8	R3.8	1,000 mg. per day for 3 days
16	3/16/44	1.3			L4.3	R4.3	1,000 mg. per day for 3 days
E. P. H.							
1	11/ 2/42	0.6	R3.0				None
2	11/ 6/42	1.4			L4.8		1,000 mg. first day, and 500 mg. per day for 2 days
F. W. M.							
1	11/ 6/42	0.2	R4.0				None
2	11/11/42	0.9			L3.5	R3.5	1,000 mg. per day for 3 days, and 500 mg. per day for 1 day
3	11/16/42	1.0			L3.8	R3.8	1,000 mg. per day for 3 days, and 500 mg. per day for 5 days
T. J. M.							
1	11/23/42	0.2	R4.3	L3.9			None
2	11/27/42	0.1	R3.7	L3.0			None
3	12/ 1/42	0.2	R2.5	L3.2			None

	4	12/ 9/42	1.3			R3.0	660 mg. per day for 8 days
	5	5/ 4/44	1.3			R3.5 L3.0	1,000 mg. per day for 3 days
	6	5/11/44	1.0			R3.0 L3.5	1,000 mg. per day for 3 days
	7	5/19/44	1.1			R3.0 L3.5	1,000 mg. per day for 3 days
A. R. K.							
	1	1/18/43	+	R4.1			None
	2	1/26/43	+			L4.1	1,000 mg. per day for 4 days, and 500 mg. per day for 3 days
	3	2/11/43	+	R4.5			None
	4	2/19/43	+			L3.7	1,000 mg. per day for 4 days, and 500 mg. per day for 2 days
	5	10/28/43	+	R3.5			None
	6	12/ 1/43	+			L3.1	1,000 mg. per day for 4 days
S. C. G.							
	1	3/ 8/44	0.8	R6.5	L.6.5		None
	2	3/10/44	0.7	R5.2	L5.0		None
	3	3/16/44	1.1			R5.5 L4.0	1,000 mg. per day for 3 days
	4	3/20/44	2.2			R5.0 L3.5	1,000 mg. per day for 3 days
	5	4/12/44	1.2	R4.3	L3.0		None
	6	4/15/44	1.6			R4.7 L5.5	1,000 mg. per day for 3 days
R. L. B.							
	1	3/16/44	0.4	R3.0	L3.2		None
	2	3/20/44	2.2			R2.2 L3.5	1,000 mg. per day for 3 days
	3	4/12/44	1.0	R3.0	L3.2		None
	4	4/17/44	1.0			R2.0 L3.5	1,000 mg. per day for 3 days
	5	4/26/44	0.6	R4.0	L2.6		None
	6	4/28/44	0.8	R3.0	L3.8		None
	7	5/ 1/44	1.0			R2.0 L4.0	1,000 mg. per day for 3 days
C. H. D.							
	1	3/16/44	0.6	R2.0	L2.2		None
	2	5/ 3/44	0.9	R1.2	L1.2		None
	3	5/10/44	1.5			R1.8 L1.8	1,000 mg. per day for 4 days
	4	5/16/44	0.8	R1.2	L2.5		None
	5	5/19/44	1.4			R2.7 L2.7	1,000 mg. per day for 4 days
	6	5/26/44	1.1			R1.7 L1.5	1,000 mg. per day for 3 days
	Average Reaction			3.6 cm.		3.3 cm.	
	Reaction			1.2 to 5.5 cm.		1.5 to 5.5 cm.	
	Average Plasma Ascorbic Acid			0.6 mg. per 100 c.c.		1.3 mg. per 100 c.c.	
	Plasma Ascorbic Acid			0.1 to 0.9 mg. per 100 c.c.		0.9 to 2.2 mg. per 100 c.c.	

++ = no determination made.
+ = excretion tests were made in these cases.
L = left arm; R = right arm.

doses. It was dissolved in cool water and drunk immediately. None of the vitamin was given on the day of the skin test.

The experiment was made on the assumption that the size of the skin reaction would change with a change in the relative state of allergy. This assumption is only partly valid, however, since it is realized that clinical allergy may in some cases improve, as in hay fever, without alteration in the size of the skin reaction. Furthermore, ephedrine, for instance, has been found to have little effect upon skin reactions, and yet it is clinically effective. The fact that ascorbic acid administration does not alter the size of wheals induced by ragweed extract is not offered as prima-facie evidence that it can be of no clinical value.

DISCUSSION OF DATA AND CONCLUSION

The data obtained in this experiment are presented in Table I. It is evident that the subjects varied a great deal in their initial plasma level, the range being from 0.1 to 1.2 mg. per 100 c.c. with an average of 0.6 milligrams. At Duke Hospital, 0.6 mg. is considered to be the lower level of normal among well-nourished adults. The forty-three skin reactions in this group varied from 1.2 to 6.5 cm. with an average of 3.6 cm. The variation between the size of the left and right arm when skin tested simultaneously was 0 to 1.4 cm. with an average of 0.6 cm. This figure may be considered the average error involved in this method of reading skin tests.

After giving the large amounts of ascorbic acid the plasma levels ranged from 0.9 to 2.2 mg. per 100 c.c. with an average of 1.4 mg. The forty-four skin reactions in this group varied from 1.2 to 5.5 cm. and averaged 3.3 cm. The variation between the skin tests of the right and left arm was from 0 to 1.5 cm. with an average of 0.7 cm.

It is obvious that there is no significant difference before and after giving the ascorbic acid in the average size of the skin reaction or the average error in reading them. The only significant difference between the two sets of data is the plasma level of ascorbic acid. After giving the ascorbic acid, the plasma level was a little more than twice as high as it was before giving the vitamin. From these figures the conclusion is that by the methods used in the experiment there is no evidence that ascorbic acid has any effect upon skin reactions due to an extract of short ragweed pollen.

SUMMARY

1. A general review is given of the conflicting opinions concerning the relationship between ascorbic acid and allergic conditions in human beings. A discussion of the rationale of ascorbic acid therapy is presented.

2. The results of an experiment are recorded in which eight young, male adults with hay fever acted as subjects. At various intervals, a total of forty-three control skin tests were made on these subjects with an

extract of short ragweed. The plasma levels of ascorbic acid were measured at the time of most skin testing. Then at various intervals large amounts of ascorbic acid were given over a period of several days and, after taking the vitamin, a total of forty-four more skin tests were made on the same eight subjects. The plasma level of ascorbic acid was likewise measured as previously. The average diameters of the erythemas of the two sets of data were compared.

3. The conclusion reached was that by the methods used in this experiment there is no evidence that ascorbic acid has any significant effect upon allergic skin reactions due to intracutaneous injection of an extract of short ragweed pollen, although it is realized that this experiment, in itself, cannot entirely prove that ascorbic acid can have no clinical value.

The author is indebted to Drs. S. C. Dees, W. A. Perlzweig, and D. T. Smith for suggestions, to Mrs. Ruth McClure and Miss Rachael Lewis for the laboratory work, and to Messrs. Holt, McCune, Moore, and Kessler (medical students) and Messrs. Dienner, Blake, and Groshong for acting as subjects.

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CEREBROVASCULAR ACCIDENTS FOLLOWING EPINEPHRINE INJECTIONS

Report of Two Cases*

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THE widespread usage of epinephrine (adrenalin) with relative impunity in allergic conditions creates a sense of security which must be sobered by the possibility of serious accidents. Although the unpleasant side reactions of anxiety, restlessness, throbbing headache, vertigo, and palpitations are recognized by all physicians, experience with more disastrous effects is limited. Awareness of the contraindications of the employment of the drug in hyperthyroid disease, hypertension, marked arteriosclerosis, organic heart disease, certain phases of shock, angina pectoris, and hypersusceptible individuals is universal. However, the potential danger of epinephrine injection in the younger age group is often overlooked.

There have been sporadic reports of cerebrovascular reactions to injections of epinephrine. As early as 1905, a description of cerebral hemorrhage in rabbits was presented by Erb.[1] Experiments have also been performed on dogs by Bouckaert and Jourdan,[2] who were able to produce vasoconstriction in the circulatory system of isolated heads. The work of Cachera and Fauvert[3] in similar experiments on dogs was in accord with these findings. More recently there have been two very interesting case reports in the American literature. In 1938, Flexner and Schneider[4] described the case of a young female who developed a subarachnoid hemorrhage shortly after the subcutaneous injection of 0.5 c.c. of 1:1,000 solution of epinephrine. They interposed as the background the possibility of a congenital aneurysm. In 1939, Keeney[5] reported a case of hemiplegia in a young white male adult immediately following an injection of a solution of epinephrine hydrochloride.

During the past year at Gorgas Hospital there have been two cerebrovascular accidents in young adult males, who received injections of epinephrine hydrochloride for the relief of asthmatic attacks.

CASE REPORTS

Case 1.—The patient, a 28-year-old white man, was in the hospital during a two-month period, under observation and treatment for bronchial asthma, due to multiple inhalants (feathers, dust, kapok). During his hospital stay he had mild recurrent episodes but response to oral administration of ephedrine sulfate was adequate. He was placed on specific desensitization and fared well until one morning, when he

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suffered a severe asthmatic attack, unaffected by ephedrine sulfate (¾ grain). A subcutaneous injection of 0.5 c.c. of a 1:1,000 solution of epinephrine hydrochloride was then given. Prior to this time, he had never received epinephrine. Within a few minutes he became restless, apprehensive, exhibited difficulty in speech, and manifested an inability to move his right upper and lower extremities. Neurological examination revealed a complete right hemiplegia with the classical findings of facial and extremity palsies due to a central lesion. Eyeground examination disclosed a moderate vasoconstriction of the retinal vessels. After several hours the findings began to subside. Treatment consisted of rest in bed and the administration of nitroglycerin in the form of tablets. After twenty-four hours, there were still residual signs of weakness of the right upper and lower extremities, right facial palsy, and slurring speech. Further questioning revealed that about one hour before the epinephrine was administered the patient noticed vertigo, some weakness of the right extremities, and a slight defect in speech. At the end of five weeks, he was practically well except for a very slight facial palsy.

CASE 2.—The patient, a young adult white man with a history of asthmatic attacks recurring for two months, was admitted to the hospital for a survey. Examination and laboratory studies were indicative of bronchial asthma, allergic in origin. Ephedrine sulfate and sedation controlled the mild symptom complex. Before a detailed study to ascertain the etiology was completed, he was seized with a moderately severe attack of asthma and was given a subcutaneous injection of 0.5 c.c. of 1:1,000 solution of epinephrine hydrochloride for the first time. After fifteen minutes, side reactions of headache, nervousness, and palpitations were noted. He exhibited mental symptoms and an inability to move his left leg and left upper extremity. There were distinct neurological findings of left facial and left extremity palsies due to a central lesion. The episode lasted more than one hour, and within two hours there was complete clearance.

COMMENT

The occurrence of cerebrovascular accidents following the injection of epinephrine is a distinct possibility, which may present itself in any age group. Although it is a comparatively rare complication, the pharmacologic action of the drug on the vascular system creates a constant threat. The modus operandi in these two cases was most likely based upon the vasoconstriction of the arterioles in the brain, producing subsequent anoxia and anemia with the attendant syndrome of hemiplegia. It was transient in Case 2, but because of an intramedullary lesion due probably to hemorrhage. It was of long duration in Case 1. In Case 1, the possibility loomed that a vascular defect (possibly congenital) produced symptoms prior to the injection, but the administra-

tion of epinephrine either induced a definite pathologic lesion, or enhanced one already present.

There are several factors which may be of importance in precipitating these accidents. The patients may be hypersusceptible to epinephrine, and it is therefore wise to employ minimal dosage. Prior to the injections, both patients had received related compounds (ephedrine), orally, and the cumulative sympathicomimetic effect is therefore another consideration. Extreme care should be exercised even in the simple technique of a subcutaneous injection, for the error of intravenous injection must be avoided. This may have occurred in Case 1, as the reaction was almost immediate. Finally, there is always the possibility of an unrecognized intracranial defect, as congenital aneurysm, which may assert itself clinically after epinephrine has been employed.

SUMMARY

1. Two cases of cerebrovascular accidents following the subcutaneous injection of 0.5 c.c. of epinephrine hydrochloride (1:1,000 solution) are presented.

2. Although the vasoconstriction of cerebral vessels is an established pharmacologic action of epinephrine, such factors as hypersusceptibility, dosage, cumulative effect, and a technical error in producing an intravenous injection and unrecognized intracranial pathology are important considerations in the production of these lesions.

3. The awareness of these possibilities and the exercise of due caution in the administration of epinephrine are recommended.

Acknowledgment is expressed to Estelle Hall, secretary in the Health Department of the Canal Zone, for her assistance in the preparation of this manuscript.

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URTICARIA CAUSED BY CHLORINATED DRINKING WATER

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IN MAY, 1940, I was asked to investigate the case of an English officer who was "suffering from giant urticaria."

CASE REPORT

Case 1.—The patient, a 40-year-old officer, submitted the information that, two years previously, he had suffered for a short time from urticaria, and that year, when transferred to a new station, he had had a violent attack. In recent weeks, particularly, large, red, itching spots had appeared on the soles of his feet, which made walking almost impossible. A protein-free diet in addition to ephedrine and calcium was fed to the patient without success. When I examined him, he had large urticarial areas on both forearms, especially on his hands, on both legs, and on the soles of his feet. These urticarial areas covered practically the entire sole on one foot. Analysis of his blood showed: eosinophiles, 7 per cent; sedimentation rate, normal; serum calcium, 11.8 mg. per 100 c.c. of serum; potassium, 16.89 mg. per 100 c.c. of serum; K/Ca quotient = 1.43 (normal = 2).

Skin tests produced no positive evidence of sensitivity to proteins. Testing with over forty various food allergins produced completely negative results, nor were there any positive indications of bacterial allergy. The single positive reaction obtained to any degree was that to common table salt. The employment of a diet low in salt content resulted in an appreciable amount of relief in that the urticarial wheals arose less frequently and were smaller than previously, but their elimination was not complete.

Since it had previously been determined that in cases of allergy increased by NaCl the predominating causative factor is the sodium ion, while the effect of the chloride ion is secondary, a diet was prescribed not only low in salt, but low in sodium ion generally, but at the same time as rich as possible in calcium. However, this diet also failed to bring about complete freedom from urticaria.

The patient was transferred to Haifa and then to Egypt where it was impossible to follow any prescribed dietetic routine. Nevertheless, no further symptoms of any kind appeared. The sole essential difference experienced by the officer in Jerusalem and his later stations, in respect to his diet, lay in the fact that after his transfer, he no longer drank natural water, but took mineral waters only (Vichy, or Spinney's Kabria Water). It occurred to him that the water in Jerusalem was possibly harmful and, as a matter of fact, on his return to Jerusalem

from Egypt he again developed severe urticaria when he drank the same water as on his previous visit.

The question arose as to which components of the Jerusalem and Haifa natural drinking waters were at fault, but which at the same time were entirely absent, or present in low amounts only, in the Kabria Water. The analysis of the three types of drinking water,* resulted in the values shown in Table I.

The most pertinent difference of the constitution of the Kabria water in comparison with Jerusalem drinking water is as follows: an appreciable decrease in chloride content, particularly NaCl (3.45 against 18.54 per 100,000 parts); a lower sulfate content, particularly $MgSO_4$; and a higher amount of $MgCO_3$ (10.88 against 1.83).

Kabria water in balneologic terminology, in view of this composition, would be classified with the group of weak "earth waters." The definition of "earth mineral waters" requires a calcium-magnesium salt content of at least one Gm. per liter, as, for example, the Wildunger Helenen spring in Germany, whose content of this salt is 2.5 Gm. per liter, as compared with Kabria's value of only 0.27 Gm.

On the other hand, the amount of NaCl contained in Jerusalem drinking water, although relatively high as compared with other waters, could exert little, if any, practical influence on the body, as the amount of NaCl per liter in such water, 0.18 Gm. compares negligibly with the daily amount of 10 to 15 Gm. of NaCl taken normally from other sources than drinking water.

In striking contrast to this, however, account must be taken of an additional factor, namely, the chlorination of Jerusalem water. For this purpose ordinary chlorine, or chloramine, has been employed by the authorities for years, as no smell of chlorine remains in the water, and there is practically no taste of chlorine present. By raising the temperature of the water, though, the chlorine is volatilized, so that it is easily understandable that such water in tea, coffee, etc., can give rise to no symptoms.

Such chlorination of drinking water as a cause of allergic responses, at least of asthma, has been reported in the literature. Watson and Kibler[1] discussed a case of drinking water as a cause of asthma and so-called functional colitis. When the patient was put on distilled water exclusively for three days, he experienced no return of asthma or colitis. Then when one drop of sodium hypochlorite solution was placed in each glass of water, wheezing promptly returned.

Philipps[2] reported a case of an asthmatic patient who observed that his attacks followed drinking of water from a certain well. This was pure well water, not chlorinated, and suspicion fell upon the lubricating oil used in the pump. I have encountered only one report, cited by

*I am greatly indebted to the Chemical Department of the Government Laboratories in Jerusalem (Mr. Baker), and to Spinney's Ltd., Haifa for this analysis.

TABLE 1

COMPARATIVE ANALYSIS OF COMPOSITION OF PALESTINE DRINKING WATERS

CHEMICAL CONSTITUENT	JERUSALEM WATER (RAS-EL-EIN)	HAIFA WATER	KABRIA (ACRE) WATER
	Parts per 100,000		
Chlorine (as chlorides	13.0	6.0	3.45
Calcium (Ca)	4.88	8.13	6.34
Magnesium	2.02	2.80	4.54
Sulfates (SO_4)	3.59	7.61	2.10
Carbonates (CO_3)	8.50	12.12	16.05
Nitrates (NO_3)	-	1.13	Traces
Total hardness (by soap)	22.0	29.4	30.36 (Wartha-French)
Permanent hardness	11.5	14.4	3.05 (Wartha-French)
Total solids at 100° C.	46.0		35.17 (At 110° C.)
Total solids at 140° C.	40.0	44.0 (at 150° C.)	28.33 (At 180° C.)

PROBABLE CHEMICAL COMBINATIONS	JERUSALEM WATER	HAIFA WATER	KABRIA WATER
		Parts per 100,000	
Calcium carbonate ($CaCO_3$)	12.08	20.20	15.85
Calcium sulfate ($CaSO_4$)	-	0.15	-
Magnesium carbonate ($MgCO_3$)	1.83	-	10.88
Magnesium sulfate ($MgSO_4$)	4.50	9.41	2.62
Magnesium chloride ($MgCl_2$)	2.27	3.52	3.44
Sodium nitrate ($NaNO_3$)	-	1.64	-
Sodium chloride (NaCl)	18.54	5.57	3.32
Potassium chloride (KCL)	-	-	0.31
Total	39.22	40.49	36.42

Dutton,[3] of drinking water as a cause of eczema, but it was impossible to determine the cause unquestionably.

The author has had the opportunity of showing, in the case of other patients, that the addition of small amounts of chlorine to natural drinking water may cause urticaria.

CASE 2.—A 28-year-old woman suffered since childhood from recurring eruptions of urticaria, which, in recent years, had become more frequent, stronger, and of longer duration, lasting for three or four weeks. Even the most extreme diet failed to prevent the eruption. The blame was initially placed on the mixed diet of her place of residence which was in an Arab vicinity where European food was popular. Ten days' residence in an outlying Arab village near her home brought complete freedom from her complaints, in spite of the fact that the patient ate all the foods ordinarily indigenous to a country residence, prepared according to Arab methods. Upon her return home, all her former symptoms reappeared in the course of a few days. There was no ground for suspecting psychological influences. Diet and a variety of medicines brought no relief. She was then brought to this clinic.

The only allergic responses shown by tests were a slight reaction to mutton and an appreciable reaction to table salt, more to the chloride component and not to the sodium component. A diet low in salt content and entirely free of meat brought only slight relief. On the basis of our experiences with the first patient, the drinking water was sup-

planted by Kabria drinking water, with the notable result that after approximately one week the patient's urticaria appeared less and less frequently, and finally disappeared completely. Upon reverting to ordinary chlorinated water, the eruptions recurred in a few days. Ordinary unchlorinated, drinking water was tolerated. Also in the previously mentioned Arab village, which was supplied directly from a well, no urticarial symptoms appeared, despite the salt-rich meat menus.

In water tanks, where the possibility of entrance of foreign substances is not entirely eliminated, suspicion must naturally be directed to other (bacterial) factors; but the water of even well-sealed tanks has always the same effect as that of poorly sealed tanks in respect to urticaria. Therefore, the chlorination of the water must be regarded as the responsible causative factor in these cases of urticaria.

SUMMARY

Two patients with urticaria and angioneurotic edema are reported. In both of these cases the chlorinated drinking water was found to be the cause of the symptoms.

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Special Reports

RECENT ADVANCES CONCERNING THE HISTAMINE PROBLEM*

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RECENT progress on the histamine problem has dealt mainly with: (a) its liberation by animal poisons (snake and bee venoms and trypsin); (b) its participation on allergic reactions in man; (c) the inhibitory effect of several substances, including thymoxyethyldiethylamine, amino acid derivatives, and histamine compounds; (d) the probable nature of its connections with the cell proteins; (e) its therapeutic effect on allergic diseases; and (f) its role on inflammation and production of gastric ulcers. We will review the recent work connected with each one of the above items. Reviews of the histamine problem have been published in 1941 and 1942 by Feldberg,[1] Dragstedt,[2] and Rocha e Silva.[3]

a. *Liberation of Histamine by Animal Poisons.*—Feldberg and Kellaway[4] were the first to attribute the ability of snake and bee venom to liberate histamine to lecithinase. The lecithinase of those venoms when placed in contact with egg yolk generates a hemolytic substance called lysolecithin which, per se is capable of liberating histamine. Trethewie[5] has shown that the hemolytic capacity of several snake venoms runs parallel with their histamine liberating capacity. The problem is complicated since the venom when placed in contact with several animal tissues generates conspicuous amounts of a pharmacologically active substance which has been named "slow reacting substance" (S.R.S.), the effects of which can be dissociated from those produced by histamine.[4] On the other hand, the venoms confer to the extracts of perfused organs the ability to liberate histamine, as the "envenomed organs" have the property to contract guinea pig intestine and produce desensitization, as well as to display some of the properties of the venom itself. Feldberg, Holden, and Kellaway[6] studied, comparatively, the effects of pure lysolecithin with those produced by substances generated in the body following the contact of snake venoms with the tissues and concluded that lysolecithin-like substances might be involved in the production of the pharmacologic and pharmacodynamic effects of snake and bee venoms. At this stage of the research, the Australian workers concluded that histamine might be released from a lipoprotein complex,

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by the interaction of any hemolytic agent capable of splitting lipoid substances of a lecithin-like character.

In 1940 and 1941, we showed[8, 9] that the whole picture of histamine liberation by animal poisons could be drawn only if one considers the fact that those venoms have also a marked proteolytic activity, since proteolytic enzymes of the trypsin type have been shown to produce pharmacologic effects which are indistinguishable from those produced by snake and bee venoms. Trypsin releases histamine from the tissues of the guinea pig lung.[7] Arellano, Lawton, and Dragstedt[9] fully confirmed our findings following experiments of perfusion of the guinea pig lung with trypsin and have shown that intravenous injection in dogs results in the appearance of considerable amounts of histamine in the blood. That this released histamine comes mostly from the liver was shown by estimating the histamine content of the liver before and after the injection of trypsin. Six to ten milligrams of histamine base disappeared from the liver of dogs submitted to trypsin shock. A quite similar discharge of histamine from the liver of dogs following anaphylactic shock was shown by Ojers, Holmes, and Dragstedt.[10]

The subsequent work, which I undertook in collaboration with Dragstedt and with Essex,[11-13] was done with the aim to amplify the proofs of a mobilization of histamine from the tissues under the action of trypsin. First, we have studied the effect of substances which are known to antagonize the effects of histamine. Arginine and histidine prevent the effects of histamine upon the smooth muscle of the guinea pig uterus and intestine[14, 15] and prevent the effect of the antigen upon sensitized structures.[16] This reaction was regarded by Ackermann[17] as proving that histamine is the chemical mediator of the anaphylactic contraction of the sensitized uterus in the guinea pig. Notwithstanding that, Kellaway and Trethewie[18] have shown that the anaphylactic response of smooth muscles must be regarded as a consequence of a release of histamine (quick response) and the release of a "slow reacting substance" (delayed response). A similar mechanism seems to hold true in regard to the contraction of the guinea pig intestine by trypsin, since in its effects we can distinguish clearly the quick response (histamine effect) and a delayed response probably mediated by a similar "slow reacting substance."[19] More recently, Trethewie[20] has shown that trypsin liberates the "slow reacting substance" when perfused through rabbit's liver. In consequence, arginine and histidine which entirely inhibit the response of the guinea pig intestine to anaphylaxis and trypsin in vitro, seem also to counteract the "slow reacting substance."

The intravenous injection of trypsin and snake venoms in rabbits results in a striking reduction of the blood histamine.[12, 13] In the case of trypsin, a leucopenia was also observed.[12] Furthermore, the addition of trypsin to heparinized rabbit's blood leads to the transfer of histamine from cells to plasma.[12] The diffusion of histamine from cells to plasma and to tissues, as well as the leucopenia which follows trypsin injection

would account for the decrease of histamine in the circulating blood of rabbits. Strikingly similar findings were obtained in sensitized rabbits which receive an intravenous injection of antigen[21] or in normal rabbits given peptone intravenously.[22] Heparinized blood samples of sensitized rabbits, when placed in contact with the antigen in vitro, also shows a diffusion of histamine from cells to plasma.[23-27] Ascorbic acid is unable to prevent this effect.[28]

Since Feldberg had shown[29] that snake venoms liberate epinephrine from the adrenals of the cat, and since epinephrine is a powerful antagonist of the action of histamine on the guinea pig lung, we tried to ascertain whether the removal of the adrenals would increase the degree of emphysema produced by the injection of crotalin or trypsin.[13] There was a definite increase in the size of the emphysematous lung after adrenalectomy plus an injection of trypsin or crotalin, but the emphysema was not so pronounced as is seen in anaphylactic shock. The observed reduction of histamine in the blood of guinea pigs treated with trypsin and crotalin, as well as the enormous hyperemia of the abdominal organs, suggested that the mechanism of death of guinea pigs given trypsin or crotalin is somewhat analogous to the mechanism of death of rabbits under similar circumstances. Consequently, the main episode of trypsin and crotalin poisoning in the guinea pig seems to develop in the circulating blood itself. On the contrary, in anaphylactic shock in the guinea pig, the main liberation of histamine takes place when the antigen enters into contact with the lung tissues. This would afford ideal conditions for the production of the emphysema and for increasing the histamine content of the blood, as shown by Code.[30]

b. *The Participation of Histamine in Allergic Reactions.*—The reaction of individuals with dermatographia is followed by secretion of hydrochloric acid in the stomach.[31] Horton, Brown, and Roth[32] described the reaction of twenty-two patients sensitive to cold and stressed the conspicuous analogy between local and systemic reactions to cold and the symptoms elicited by injecting histamine. Also an increased secretion of free hydrochloric acid in the stomach of patients sensitive to cold following immersion of one hand in cold water was reported.[33, 34] In an extensive study of the histamine content of normal human blood, Rose and Browne[35, 36] have found an average histamine content of 4 volumes per 100 c.c. of blood, with variations from 2 to 75 volume. Repeated determinations on the same person have shown that the normal histamine content is fairly constant, with only minor variations. Rose[37] studied the effects of stimulating the skin of fifteen patients suffering from a wide variety of skin sensitivities. There were ten cases of dermatographism, three of allergy to cold, one of allergy to heat, and one of hypersensitiveness to light. In two cases of dermatographism, there was a definite increase of the histamine content of the blood following wheal formation; in three cases, only a slight increase; and no change occurred in five cases. A definitely increased histamine content appeared in two

patients with cold allergy following application of cold, while the third case of cold allergy and the only case of photosensitivity did not show any variation of the histamine content following application of either cold or ultraviolet light. Interesting enough was the fact that twenty to thirty minutes after application of the stimulus to the skin and consequent formation of wheals in three patients who had shown an increase of the histamine content of the blood, there was a definite lowering below the normal mark. Rose could not fail to make a comparison between this lowering of the histamine content of the blood after exposure to skin irritants with the results described previously by Rose and Browne[35] of a decrease of the histamine content following surgical shock. This same decrease of blood histamine was shown by Rose[38] to occur in cases of angioneurotic edema following appearance of the symptoms. Rose studied the variations of the histamine content of the blood in eighty patients with asthma, urticaria, angioneurotic edema, eczema, hay fever, and allergic colitis. In contrast with what occurs in the normal individual, the histamine level in allergic patients shows enormous fluctuations in the course of many months or years. Although, in most cases, these variations did not bear any relationship with the development of symptoms, they showed a certain degree of lability of the connections of histamine with the tissues of allergic patients, contrasting with the stability of the same connections in normal individuals.

On the basis of Rose's findings, one might interpret the somewhat contradictory results described by many workers on histamine estimations in the blood of allergic patients. Cerqua[39] found an increase of blood histamine in asthma. Capps and Young[40] reported an increase in the blood histamine of a patient with photosensitivity, following exposure to ultraviolet light. Code and Mac Donald[41] reported cases of eosinophilia with a blood histamine content definitely above the normal range. Rose[26] has shown an increase of the histamine content of the blood in patients with eosinophilia, while in other patients showing the same symptoms, the blood histamine was definitely below the normal. Parrot[42] reported an increase of histamine level in the blood in four cases of bronchial asthma, from three to four times the normal value. Capuani[43] reported also an increase in the blood histamine following asthmatic attacks. Randolph and Rackemann[44] found an average of 45 volume of histamine per 100 c.c. of blood in twenty normal individuals with a range of variation from 19 to 71 volume per 100 c.c. There was a definite increase of the histamine content of nine patients with bronchial asthma during the development of the symptoms, compared with the levels found in the intervals between the attacks. They did not find, however, any significant correlation between eosinophilia and the histamine level in the blood, which contrasted with previous findings of Code and Mac Donald.[41] In five of the eight cases studied by Randolph and Rackemann, the eosinophile counts were conspicuously higher than those reported by Code and Mac Donald, and, nevertheless, there was

no increase of the blood histamine above the normal range. In cases of allergy to hydatic fluid, Graña et al.[45] reported an increase of the blood histamine far above the normal level.

From the above findings, one might conclude that the histamine connections with the cell constituents is more labile in allergic individuals and that the release of histamine frequently follows the onset of allergic symptoms. More definite proofs of a release of histamine by contact of the allergic tissues with the allergen was shown by Katz and Cohen.[46] Heparinized blood collected from humans with pollen and dust allergies were placed in contact in vitro with extracts of the respective allergens. A definite shift of the histamine, previously bound to blood cells, to plasma was observed. While the contact of the blood samples with the allergen resulted in several cases in minor increases of the plasma histamine (from 60 to 76 per cent), in most of the cases the increase of plasma histamine ranged from 168 to 900 per cent. More recently, Katz[47] has devised an ingenious method to show the histamine release from the skin in allergic individuals when extracts of the allergen entered in contact with the living cells of the lower layers of the skin exposed by previous application of cantharidin and subsequent removal of the epidermal layers.

c. *The Inhibition of the Histamine Effects.*—Symptomatic therapy of allergic diseases consists mainly in counteracting effects which might be concerned with the pharmacologic effects of released histamine. Besides the specific (desensitizing or hyposensitizing) therapy, the whole problem of relieving allergic symptoms deals mainly with: (a) finding a substance which antagonizes the histamine effect, and (b) increasing the resistance of the system to histamine, by repeated injections of a small dose of this substance (nonspecific desensitization). These are strong arguments for the histamine theory of allergic diseases.

Epinephrine is the best antagonist of the effects of histamine upon smooth musculature.[48] Epinephrine seems to counteract the increased permeability of the endothelial wall, produced by xylene application or injection of staphylococci suspensions into the rabbit skin[49, 50] and to interfere with allergic skin tests.[51] As regards the effect of epinephrine upon the triple response produced by histamine in human skin, Barroso[52] described experiments showing that epinephrine (1:2,000 solution) when injected with histamine (1:4,000 solution) definitely impairs the development of the wheal produced by the latter. If epinephrine is injected two or three minutes before histamine, the wheal is almost entirely prevented. Barroso concluded therefrom that histamine acts more quickly than epinephrine on the small vessels of the skin and, if time is allowed for epinephrine to act, the antagonism against histamine whealing can be easily observed. Aminophylline (75 to 82 per cent of theophylline plus 12.3 to 13.8 per cent of ethylenediamine) was found by Young and Gilbert[53] to counteract the bronchospastic effect produced

by histamine on guinea pigs. Emmelin, Kahlson, and Lindstroem[54] reported the antihistamine effect of xanthine derivatives (xanthine, theobromine, caffeine, theophylline, and aminophylline) as well as their antianaphylactic effect on sensitized smooth muscles. Using the trypan blue test in rats, Hechter[55] did not find any potentiating effect of removal of the adrenal glands on the action of histamine on the permeability of the rabbit skin capillaries. According to Hechter's experiments, histamine had no effect on the permeability of the muscle capillaries of the rat.

Staub[56a] and Bovet and Staub[56b] tried a number of products which have been synthesized in Fourneau's laboratory. Among those, they found that 929 F (thymoxyethyl*di*ethylamine) and 1571 F (*N*-phenyl-*N*-ethyl-*N'*-*di*ethylethylene*di*amine) were most useful in counteracting the histamine effects on the guinea pig intestine and lung and on the circulatory apparatus of the rabbit. The usefulness of 929 F was confirmed by Rosenthal and Minard.[57] The compound 929 F was found by Bovet and Staub[56b] to counteract anaphylactic shock in the guinea pig, and this was confirmed by Rosenthal and Brown.[58] Thymoxyethyl-*di*ethylamine was found by Loew and Chickering[59] to decrease the secretion of gastric juice produced by injecting histamine in normal dogs, while no effect was observed on secretion of Heidenhain's pouches in similar circumstances. Further experiments have shown that 929 F and 1571 F do not affect the gastric secretion produced by administration of histamine to normal dogs or to dogs with Heidenhain's pouches[61] but they definitely inhibit the secretion of gastric juice produced by a meal, whatever may be the kind of gastric operation to which the animal had been submitted.[62] A decrease of the motility of the duodenum produced by thymoxyethyl*di*ethylamine was reported by Hallenbeck, Code, and Mann.[63] The product 1571 F was also tried by Wilcox and Seegal[64] as an antihistamine substance to counteract the effects of histamine and of anaphylactic shock on the intact guinea pig and the isolated guinea pig heart.

Extremely interesting results have been reported by Sheldon, Fell, Johnston, and Howes[65] on the inhibition of the histamine effects by previously treating allergic individuals and sensitized animals, with a complex antigen of histamine with horse serum globulin. Histamine is bound to an intermediary aryl amine which can easily be bound to despeciated horse globulin, after diazotization. Animals and humans immunized with this antigen-H acquire a powerful ability to detoxify histamine, as reported by Cohen and Friedman,[66] and a definite increased resistance to anaphylactic shock and to the histamine locally released after combination of the antigen with the antibody in sensitized rabbits.[67] Quite similar results with a synthetic antigen prepared by coupling the isocyanate derivative of histamine with despeciated serum globulin are described by Rodney and Fell.[68]

In 1937, Edlbacher, Jucker, and Baur[14] had shown that several amino acids (arginine, histidine, and cysteine) counteract the effects of histamine on the isolated guinea pig intestine. In 1939, Ackermann and Wasmuth[15] fully confirmed the results of the previous investigators and demonstrated that, even in combination with other amino acids to form complex protein molecules (as clupein which contains 80 per cent of arginine), arginine inhibits the histamine effects on smooth muscle structures. From extensive studies on arginine derivatives, Ackermann concluded that the guanidyl radical, present in the arginine molecule, is responsible for the antihistamine effect. On basis of those findings, Ackermann[17] assumed that the = NH imine group present in arginine and in the imidazol ring of histidine, would compete with like = NH group of the imidazol ring of histamine. According to this theory, this imine = NH radical would be the anchoring group for the histamine to the chemical receptors of smooth musculature. If a considerable excess of either arginine or histidine is previously added to the perfusing bath, histamine would have no chance to combine with the saturated chemical receptors and consequently to produce its characteristic stimulant effects.

The interest of this theory is the suggestion of a definite separation between the toxic effects of histamine (which depends on the $-NH_2$ amine radical) and its anchoring ability to the cell receptors (depending on the $=NH$ imine radical of the imidazol ring). The possibility of separating these two functions of histamine would enable one to block the grouping that is responsible for the pharmacologic effect and, at the same time, to keep unchanged the capacity for histamine to anchor upon the chemical cell receptors. This might provide a class of histamine derivatives as effective in inhibiting the histamine as are arginine and histidine. Those conditions were fulfilled in the five compounds of histamine with amino acids that we have been able to synthesize in Dr. Bergmann's laboratory, at the Rockefeller Institute.[69] The acetyl-dehydrophenylalanyl-histamine, the carbobenzoxy-l.tryosyl-histamine, the benzoyl-l.tyrosyl-histamine, the acetyld,l.phenylalanyl-histamine and the carbobenzoxy-l.leucyl-histamine are entirely devoid of pharmacologic activity while still having an uncombined imidazol ring. This shows that blocking the $-NH_2$ amine radical through chemical combination with the carboxyl groups of amino acids, would destroy the pharmacologic activity of histamine. On the other hand, the fact that the imine radical ($=NH$) of the imidazol ring is kept free in those compounds, would indicate that they might compete with free histamine in its anchoring capacity upon the cell receptors. This assumption was fully verified, since those compounds display an antihistamine effect on the isolated guinea pig intestine, of the same order of magnitude as do certain arginine derivatives and histidine hydrochloride.[70] We have also studied the antihistamine effect of several arginine compounds as benzol-l.arginine-amide, benzol-l.arginine, arginine monohydrochloride and hip-

puryl-nitro.l.arginine. Since it has been shown by Ackermann and Wasmuth[15] that argininic acid has no antihistamine effect, the following series of decreasing inhibitory potency seems to hold true for arginine, histidine, and histamine derivatives:

> Benzoyl-l.arginine-amide = histidine monohydrochloride = histamine derivatives > benzoyl-l.arginine > arginine monohydrochloride > argininic acid.

This shows that blocking the α—NH_2 or the —COOH groups, or both, definitely increases to a certain maximum the antihistamine effect of arginine compounds. This maximum antihistamine activity, corresponding to the effects of benzoyl-l.arginine-amide, histidine monohydrochloride and histamine derivatives, is probably related to an entirely free hand activity of the imine = NH radical, in saturating the cell chemical receptors. All these facts lend support to Ackermann's view[17] that the anchoring group for histamine is the = NH imine radical of the imidazol ring. The interest of this work has been to define, precisely, the two functions of histamine. The anchoring part of the molecule (haptophorous) would be the imidazol ring, and the part responsible for the pharmacologic effects (toxophorous) would be the lateral chain.

It is not difficult, on basis of these findings, to interpret the results of Alles, Wisegarver, and Shull[71] concerning inhibition of the pharmacologic activity of histamine by introducing methyl groups in α— and 5—(imidazol) positions, since one might destroy the histamine activity by blocking either its toxophorous or its haptophorous function.

Regarding the practical use of arginine and histidine as antihistamine drugs, the results[70] have been somewhat deceiving. To counteract the effect of approximately 0.02 to 0.05 volume of histamine base, one has to add 5 to 10 mg. of arginine or 2 to 3 mg. of histidine monohydrochloride. This ratio, 250,000:1, for the antihistamine effect of arginine, suggests that one would have to inject 50 to 100 Gm. of arginine intravenously to protect against one minimum lethal dose of histamine for a guinea pig of 400 to 500 grams, body weight. This explains the failure of arginine to protect guinea pigs against the lethal effects of histamine, as well as the poor antihistamine effect of arginine when tried on intact dogs. On basis of these findings, it seems rather unlikely that arginine might have any significance for the treatment of allergic diseases, since one would have to inject huge amounts of it to counteract the effects of even small amounts of histamine liberated from the tissues.

As regards histidine, Edholm[72] has shown that long treatment of cats with histidine might contribute to the reduction of the sensitivity of this animal species to the histamine effects. One explanation for this finding might be the fact that histidine as a rule contains traces of histamine. Consequently, the increased resistance against histamine after chronic histidine administration might be due to an increase of

resistance produced by chronic administration of traces of histamine as obtained in guinea pigs by Farmer,[73] Karady,[74] Essex and Horton,[75] and others.

d. *On the Nature of the Linkages of Histamine With the Cell Proteins.*—The five compounds cited previously, in which histamine was chemically bound to l.tyrosine, dehydrophenylalanine, d,l.phenylalanine and l.leucine, forming a peptide linkage with the carboxyl —COOH groups of the named amino acids, were suggested as *chemical models* for bound histamine.[69] They are pharmacologically inactive upon the guinea pig intestine, the circulatory apparatus of the cat, and the human skin. After acid hydrolysis, however, histamine is discharged and resumes its full activity. Feldberg[1] assumed that the release of histamine by antigen in anaphylactic shock might be due to activation of cellular proteinases, by exclusion of antiproteinases supposedly present in all living cells. It is interesting to note that the liberation of histamine in the above compounds was performed by rupture of a peptide linkage as would happen in the living cell by activation of proteolytic enzymes.

There are many indications in old and recent literature that proteolysis might be a prelude of the anaphylactic crisis. Friedemann and Isaac[76] have shown an increased excretion of nitrogen following anaphylactic shock. Similar results were achieved by Abderhalden and Pinkussohn[77] and Pfeiffer and Mita[78] who have shown the appearance of products of enzymatic splitting of proteins in the circulating blood of sensitized animals submitted to shock. This enzymatic splitting of blood protein was ascribed to the action of specific defense ferments mobilized as a consequence of the combination of the antigen with the antibody. What is specific in this phenomenon is probably the immunologic reaction, and not the enzymes themselves. Pfeiffer and Jarisch[79] confirmed those previous findings and have shown that the ability of the antigen to activate a proteinase in plasma appears very soon during the sensitization period and lasts for thirty days. In 1913, Vaughan[80] stated: "We hold that sensitization develops in certain body cells a new function—that of elaborating a new specific, proteoclastic ferment." Jobling and Petersen[81] showed that specific precipitates can activate plasma trypsin by adsorption or inactivation of plasma antitrypsin. In more recent times, Miller[82] verified an increased excretion of nitrogen in dogs submitted to anaphylaxis, and Dragstedt, Wells, and Rocha e Silva[83] have shown that heparin inhibits both proteolytic action of trypsin and the ability of peptone, trypsin, and antigen of liberating histamine from normal or sensitized rabbit blood cells.

With the general acceptance of the cellular theory of anaphylaxis as developed by Dale,[84] the old conception of proteolysis as generating toxic products in the plasma had a serious setback, and it was not until very recently that a comprehensive theory of anaphylaxis depending on an activation of proteolytic enzymes could be restored.[1] The possibility

of liberation of histamine by activation of cellular cathepsins is turning now to be a very attractive viewpoint, since a proteolytic enzyme like trypsin has been found to duplicate all the features of anaphylactic shock, when injected intravenously to most animal species.[8, 9] We dispose now of strong evidence that histamine is bound to cells forming peptide bonds with the amino acid chain of tissue proteins. This peptide bond seems to display a definite specificity toward proteolytic enzymes of thebenzoyl-l.arginine amide type. First, trypsin whose specific substrate is benzoyl-l.arginine-amide or benzoyl-l.lysine-amide is one of the most powerful substances which liberate histamine. Chymotrypsin which does not split those substrates is practically devoid of the capacity of liberating free, active histamine from cells. Finally, we have been able to fractionate papain at pH 7.3 to 7.5 and to show that the ability of this ferment to liberate histamine runs parallel to its ability of splitting benzoyl-l.arginine-amine.[85] These facts would suggest that most of the histamine present in living cells is bound to arginine or to lysine and can be liberated by the action of a ferment displaying the specificity of trypsin. If one extends these findings to the cathepsin system of living cells, it would probably be cathepsin II, the proteolytic enzyme which might liberate histamine when an activation of intracellular cathepsins should be expected, since the specific substrate for cathepsin II, is benzoyl-l.arginine-amide or benzoyl-l.lysine-amide, as shown by Fruton, Irving, and Bergmann.[86]

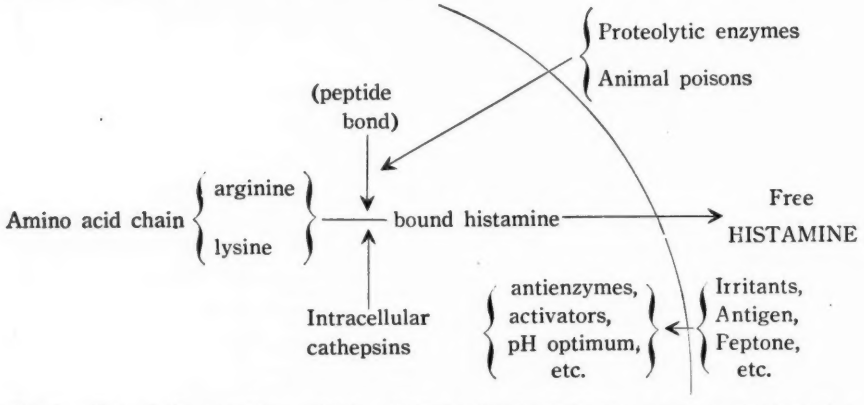

Fig. 1.—The chain reactions which might be involved in the process of histamine liberation.

On basis of this discussion, the scheme of Fig. 1 was drawn[87] in an attempt to visualize the possible connections of histamine with the cell proteins and the chain reactions which might be involved in its liberation. Two distinct groups of histamine liberating substances might be clearly set forth: (a) substances which would act indirectly by activating the cell cathepsins, and (b) substances such as proteolytic enzymes and animal poisons which might act directly by rupturing the peptide linkages of histamine with the cell proteins.

Put on this basis, the mechanism of release of histamine, many possibilities might arise for a practical and rational attack to the problem of inhibiting this release. The most urgent question would be to investigate if and how cell cathepsins are activated by combination of antigen with antibody. This certainly is a new and attractive approach to a most important problem.

e. *Histaminase and Histamine Therapy.*—A histaminolytic ferment (histaminase) was shown by Best and Mc Henry[88] to destroy histamine only in presence of oxygen. This was confirmed by many workers.[89, 90] Hydrocyanic acid also inhibits the effects of histaminase. Edlbacher and Zeller[89] suggested that histaminase is an hemin, and Zeller[90, 91] showed that histaminase can destroy other diamines, as cadaverine and putrescine. Following biologic inactivation of histamine by histaminase, Zeller, Schaer, and Stählin[92] assumed that one atom of oxygen is consumed and NH_3 and H_2O_2 are produced, according to the equation:

$$R.CH_2.CH_2.NH_2 + O_2 + H_2O \rightarrow R.CHO + NH_3 + H_2O_2$$

Zeller, Stern, and Wenk[93] reported that aldehyde was produced during histaminase-histamine reaction, this being proof of the validity of the above equation.

The amount of oxygen consumed to inactivate one molecule of histamine, was found to depend on the state of purity of the histaminase preparation,[94, 95] the purest preparations catalyzing the consumption of one atom of oxygen per molecule of histamine. Recently, Stephenson[96] confirmed these findings by using a very purified preparation of histaminase from hog kidney cortex and showed that, when histaminase acts upon one molecule of an aliphatic diamine, one molecule of ammonia is liberated, one molecule of aldehyde is formed and one atom of oxygen is utilized. Evidence is presented that hydrogen peroxide is also formed during this reaction.

Histaminase acts very slowly in vitro, but there are indications that in vivo its action is much accelerated.[97] Doubt is aroused as to whether or not this ferment is the only tool employed by the organism to detoxify histamine. That a simple capture of histamine by lung tissues might contribute to detoxify histamine has been shown by Ahlmark, Kornerup, and Tarras-Wahlberg[98] and that this capture might be due to chemical combination with free —COOH groups of cell amino acids was also suggested.[69]

Attempts to bring histaminase into general practice as a therapeutic agent against allergic diseases have been reported. Successes, as well as complete failures were obtained with histaminase therapy. A review on the subject up to 1940 is given by Roth and Horton.[99] Complete failure in the experimental use of histaminase to reduce the histamine content of the tissues is reported by Dragstedt.[100] There is general feeling that histaminase therapy is rapidly going into discredit. Recently,

Eustis[101] suggested that histaminase might act by reducing the histamine content of the digestive tract, when oral histaminase therapy is applied.

Histamine discharges epinephrine from the suprarenal glands[29, 102] and this might contribute to explain how minute amounts of histamine repeatedly injected in guinea pigs bring about an increased resistance of the animal to subsequent injection of one minimum lethal dose of histamine. This desensitization to histamine has been verified by many workers[73-75] and constitutes the basis of the unspecific desensitizing treatment of allergic diseases. This histaminotherapy is entering in general practice, and the results reported are fairly good. The first reference of the use of histamine in the treatment of asthma, was reported by Ramirez and St. George.[103] From that time on, histamine has been used in the treatment of migraine,[104] cephalalgia,[105] urticaria,[106-110] cold allergy,[32, 33, 111-114] bronchial asthma,[115-120] vasomotor rhinitis and hay fever,[108, 119, 121] Ménière's disease,[122, 123] etc.

That desensitization against histamine does not depend on a production of specific neutralizing antibodies is suggested by the fact that hydrochloric acid secretion of the stomach following histamine stimulation, is not affected by prolonged treatment with histamine, as shown by Stroembeck[124] and by Wells, Gray, and Dragstedt.[125] A physiologic antagonistic mechanism developed after repeated injections of histamine was suggested by Adarii[126] and might better explain desensitization to the pharmacologic effects of histamine.

f. *Miscellaneous.*—The role played by histamine during the first stages of acute inflammatory reaction was recently reviewed.[3] Lambert and Rosenthal[127] refer to experiments showing that histamine is discharged from the skin following application of irritants like chloroform and xylene. This provides a direct proof of the contention made by Bier and Rocha e Silva[128] and Rocha e Silva and Dragstedt[129] that accumulation of trypan blue in areas of rabbit skin treated with histamine liberating substances (snake and bee venoms, trypsin, Bacto-protone, irritants, etc.) depends on increased endothelial permeability produced by released histamine.

Zon, Ceder, and Crigler[130] have shown that inflammatory lesions of rabbit skin show two to ten times as much histamine as normal skin from the same rabbit. They correlated this increase of histamine in the skin of rabbits to collection of blood platelets at the site of inflamed tissues. Similar increase of the histamine content in rabbits skin was reported following allergic inflammation,[131] Schwartzman phenomenon,[132] and irradiation with ultraviolet light.[133] Shimkin, Zon, and Crigler[134] have shown that histamine is within normal limits in the blood of patients with gastric carcinoma and with peptic ulcer and have also shown a definite relationship between granulocytes and the histamine content of human blood, suggesting that histamine is bound to this special kind of blood cell. Haas[135] also reported an increase of the histamine content of the skin following application of irritants (mustard oil,

cantharidin, croton oil, turpentine, colchicine, etc.). Dragstedt[136] has shown that histamine potentiates rabbit skin to digestion in vivo by trypsin.

Histamine administered in beeswax mixtures produces tremendous amounts of hydrochloric acid secretion by gastric pouches in dogs.[137] This continuous flow of free hydrochloric acid for long periods of time was suggested by Hay, Varco, Code, and Wangensteen[138] to be the cause of gastric and duodenal ulcers produced in cats, dogs, guinea pigs, ducks, monkeys, calves, and other animals, following administration of histamine in beeswax.

Adrenalectomy definitely increases the histamine content of the gastrointestinal tract, the liver, and the lung of rats.[139] Thyroidectomy was shown to decrease the histamine content of the skin, the liver, and the lung of rats, while feeding thyroid extracts was shown to produce an increase of the histamine content of the same organs.[140]

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THE SIGNIFICANCE OF ANTIBODIES IN HYPERSENSITIVE STATES

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THE purpose of this review is to appraise the present status of antibodies in anaphylaxis, in hypersensitiveness of infection, and, particularly, in hypersensitiveness of the pollen type in man.

Phenomena currently and not always accurately referred to as "allergy," "atopy," "anaphylaxis," and "immunity," have an identical underlying mechanism although some immunologists are not in accord with this conception. Therefore, an effort will be made to clarify the conflicting interpretations of these terms by citing classical experiments. In a résumé of this limited scope it is not possible to review all papers at length; therefore, those having greater interest in so far as their clinical implications are concerned will be considered more fully.

Dragstedt[32] quotes Zinsser to the effect that "allergy in man is based on an immunological mechanism basically identical with anaphylaxis in animals, superficially modified by anatomical and physiological conditions." Dragstedt thinks there are no major inconsistencies to this assumption.

ANAPHYLAXIS

Recapitulation of a few pertinent facts reviewed by Gay[38] is necessary, and will serve as an introduction. Animal species vary greatly in the ease with which they are rendered sensitive. Individual members of a species may vary also in this respect. Furthermore, the relation of anaphylaxis to "immunity" may differ in different species of animals.

"Antibodies to the harmless proteins are not unreservedly accepted as indicative to true 'immunity' although their modes of formation and action are, in so far as we are aware, identical with those antibodies of more teleological import" (Gay[38]).

Bronfenbrenner[9] states: "Phenomena called 'immunity' and 'anaphylaxis' are, in fact, merely different expressions of the same basic process of antigen-antibody union. Difference in the final outcome depends only on the extent and speed of this union and consequent intensity of the injury to the host." He refers to the fact that a sensitized guinea pig may be killed if a lethal rose of egg white is given intravenously, but, if the same amount is diluted and given very slowly, or if the total surface of the antigen available is reduced by adsorption on collodion particles, the animal will survive, showing only mild symptoms of shock.

He remarks: "The state of refractoriness, or the state of anti-anaphylaxis has been erroneously called 'desensitization.' In fact, the animal has lost little or none of its sensitivity. It will still respond specifically to antigen, provided a sufficient amount of the latter is injected." The three terms "antianaphylaxis," "refractoriness," and "desensitization" mentioned above will, of necessity, be used interchangeably in this review, but the term "immunity" will refer only to immunity to infection. The term "allergy" will not be used except where it is quoted, or in the sense as originally defined by von Pirquet.[54]

Minute amounts of antigen suffice to sensitize the guinea pig, while the dog and rabbit are best prepared by larger, multiple sensitizing injections. Even then they may only show mild symptoms of shock, rather than violent shock or death. Guinea pigs are sensitive months after injection of a small amount of antigen when there are no demonstrable antibodies in the serum. The following facts from Gay[38] are concisely stated. Matsumoto[46] found that, in guinea pigs sensitized with horse serum, precipitins were present in high concentration in the organs, notably spleen, liver, and kidney, even when they had disappeared from the circulation. At such a time the animal was particularly susceptible to anaphylactic shock.

It should be emphasized that the factor which largely determines the severity of the injury in anaphylactic shock is the rapidity of the union of antigen and antibody in vivo (Bronfenbrenner[9]). Bronfenbrenner's elucidation of the fundemental principles involved in hypersensitive states is a worth-while contribution to this subject.

Testing passive sensitization, Gay and Southard found that the serum of certain animals, refractory against a foreign protein (as a result of repeated or large doses), was even more efficacious for transferring sensitiveness to this protein. The quantity of serum necessary to effect this transfer of sensitiveness was inversely proportional to the precipitin titer of the serum. That is, rabbit serum of high titer will transfer sensitiveness to a guinea pig in a dose of 0.1 c.c., whereas a serum with a low titer or no demonstrable antibody, must be given in a much larger quantity in order to induce sensitization.

The one known exception to this is an experiment performed by Manwaring, who found that a dog which is refractory by repeated injections of serum cannot be shocked three weeks later. Its blood then has the property of desensitizing a hypersensitive dog after a latent period of twenty-four to forty-eight hours. Manwaring states, however: "If the transfused animal is subjected to immediate anaphylactic test, no suggestion of desensitization is demonstrable." Moreover, the organs of such a refractory dog fail to react to "anaphylatoxin" released from the liver of a hypersensitive dog, following intravenous injection of antigen. The precipitin content of the serums of the refractory and hypersensitive dogs were about equal. He therefore concluded that "anaphylaxis" and "immunity" were distinct phenomena depending

on different antibodies, and one might look upon these two phenomena as differently related to one another in different species of animals. If true, then the dog possesses a mechanism which is apparently absent in the guinea pig. (This was reviewed by B. C. Seegal.)

Dragstedt[29, 32] discusses the significance of the liberation of histamine, heparin, and choline in anaphylactic shock. With the exception of incoagulability of the blood, he thinks that "the liberation of histamine can account for practically all of the other effects." "The cardinal symptoms of anaphylaxis can thus be explained as being due, in the immediate instance, to an intoxication by physiologically active substances (anaphylatoxins) normally resident in various tissue cells and liberated therefrom by some change in cellular permeability brought about by the antigen-antibody reaction." He states that it is not known how tissues become tolerant to such substances as histamine.

A large part of the more recent work on the relation of histamine to anaphylaxis in dogs has been done by Dragstedt[31] and Dragstedt and Mead,[25] but, since this review deals chiefly with the role of antibodies, the references only will be given.

It would seem that in the field of clinical hypersensitiveness, at least, an overemphasis has been put upon the role of antibodies. It is beginning to be recognized that cellular and metabolic phenomena are of equal importance, especially in the field of bacterial hypersensitiveness.

Subsequent to 1935, the following experiments, suggested by Bronfenbrenner, were undertaken by Morris,[49] and are pertinent to a number of other papers reviewed here. At this time, the accepted view concerning the mechanism of hypersensitiveness was that symptoms occur when antigen combines with fixed but not with circulating antibody. Morris[49a] studied first the role of excess of circulating antibody and secondly,[49b] the effect of specific desensitization upon resistance to infection and antibody balance. Weil[78] and others[22] considered that excess of circulating antibody reduced the hypersensitive response by preventing access of antigen to the sensitized tissues, but other investigators[34, 36] were unable to confirm this. Weil's theory was based on the fact that animals sensitized with large injections became sensitized more slowly and were shocked less easily. He attributed this to circulating antibody. His failure to establish a degree of reactivity in animals sensitized with large amounts of antigen, as compared with those sensitized with a small mount, Morris believes, may possibly have been due to persistence of antigen in animals undergoing active sensitization. Antibody may be demonstrated before all antigen has been eliminated from the circulation and hence conditions for specific desensitization are present. Furthermore, traces of antigen remaining in an antiserum, injected intravenously into an already hypersensitive animal, may cause some degree of specific desensitization.

It was observed in these studies that *normal serum* protects against a few lethal doses of antigen, and that protection is greater with foreign than with homologous serum.

Passively sensitized guinea pigs, reinjected with antibody-containing serum, preliminary to intravenous injection of antigen, showed no greater refractoriness to anaphylaxis than those injected with normal serum. In fact, these sensitized animals, which had received additional specific antibody previous to introduction of antigen, failed to tolerate even two minimal lethal doses of antigen, and two did not tolerate one-half and one-fourth of a minimal lethal dose respectively. He therefore concludes that additional antibody *enhances* sensitivity, and that this enhancement would be even greater if not for the fact that homologous or heterologous serum by itself tends to decrease reactivity. This decrease in reactivity is proportional to the amount of normal serum injected. This experiment demonstrates that "excess of circulating antibody is not responsible for a state of antianaphylaxis, but, on the contrary, may contribute toward the anaphylactic reaction itself." The experiments "tend to invalidate the idea that anaphylaxis is due to fixed antibody alone, and that refractoriness to anaphylaxis is due to circulating antibody."

According to Morris, there are facts incompatible with the hypothesis that specific desensitization exhausts or neutralizes the antibody responsible for hypersensitiveness.

In order to determine whether the effect of desensitization was due to saturation of cellular antibody, guinea pigs were passively sensitized, desensitized, and later resensitized. Their response to the parenteral introduction of antigen was then compared with that of normal animals, passively sensitized with same amount of antiserum. The resensitized, antianaphylactic animals withstood at least forty times the amount of antigen which killed normal animals. Antihorse and antipneumococcus sera were used for sensitization. "This suggests that antibody depletion is not an adequate explanation of the effect of desensitization, since, if this were so, it might be expected that desensitized animals would have become at least as highly sensitive as normal animals on receiving the same amount of antibody."

In another experiment of this type, a different serum (antihorse) was used for resensitizing animals previously sensitized with anti-Freidländer's bacillus, Type B, and antipneumococcus Type II serum, and subsequently desensitized. Again, it was observed that the same degree of reactivity was not obtained in test animals as exhibited by normal controls sensitized with antihorse serum. "These facts would appear incompatible with any theory which maintains that neutralization of fixed and circulating antibodies is the principal cause of anti-anaphylaxis. Such refractoriness to anaphylaxis is occasioned by non-specific changes in the animal."

Making use of the fact that, in the case of Freidländer's bacillus, Type B, type specific immunity, and type specific hypersensitiveness are due to the same type specific antibody, another experiment was tried. Type specific carbohydrate of Friedländer's bacillus, Type B, and type specific antiserum were used. It was found that carbohydrate-desensitized animals remained as resistant to infection as those not desensitized. A change in anaphylactic response should be accompanied by a change in immune response, provided these changes depend on antibody balance.

A determination of antibody content of serum of sensitized, as well as desensitized guinea pigs, by mouse-protection tests, indicates that a loss of reactivity in desensitized animals cannot be adequately accounted for on the basis of depletion of antibody. The author concludes that "hypersensitiveness and resistance to infection are different manifestations of the antigen-antibody reaction, while antianaphylaxis is a state of refractoriness which is due neither to excess of circulating antibody nor to antibody depletion, but is the result of secondary changes, the true nature of which is not definitely established."

More recently, Kabat and Landow,[41] who made a quantitative study of anaphylaxis in the guinea pig, found that only about 0.03 mg. of antibody-N need be present in the tissue of a guinea pig for fatal anaphylaxis. The serum of such a guinea pig would not be expected to show the usual serologic tests for antibody.

The values obtained in these experiments hold true only for passive anaphylaxis in the guinea pig, using rabbit antibody.

These facts, according to Kabat and Landow, have implications in the field of clinical allergy, where no demonstrable antibodies are evident in the patient's serum by in vitro methods, although passive transfer tests show the presence of skin sensitizing antibodies, commonly called "reagins."

Cannon and Marshall[11] nevertheless, who developed a method of coating collodion particles for demonstrating precipitation by dilution of serum, instead of dilution of antigen, demonstrated precipitins in the sera of patients sensitive to egg albumen. Such precipitins could not be shown by other in vitro methods.

Bronfenbrenner[9] believes that "failure to demonstrate circulating antibody does not indicate that sensitivity is due to 'reagin' as distinct from ordinary antibody."

In Kabat and Landow's experiments, fifty times as much egg albumen was needed to produce anaphylaxis in a guinea pig passively sensitized with 0.03 mg. antibody nitrogen, as would be required to precipitate this amount of antibody in vitro. They state that "anaphylactic reactions, therefore, have their optima at the extreme antigen excess end of the precipitative zone where soluble antigen-antibody compounds are formed and in which all the reactive groupings on each antibody molecule are combined with antigen."

They believe that these findings suggest a possible mechanism of desensitization (for the guinea pig). "When small amounts of antigen are used to desensitize, the available antibody molecules react with a fewer number of antigen molecules, producing a very slight effect. However, since antigen and antibody can combine in multiple proportions very few antibody groupings are left free and hence a fatal reaction does not occur when a large amount of antigen is subsequently injected."

This theory is not in concordance with the findings of Morris.

Burden[10] studied the changes in the antitryptic power of the blood associated with anaphylaxis in guinea pigs, using a new procedure which he developed, called the Film-disc method. He states his belief that natural antitrypsin of body fluids plays a determining role in anaphylactic reactions. The antitryptic titer increased during the incubation period, and dropped following intracardial injection of antigen into sensitized guinea pigs. Those animals surviving shock had in their serum an especially high content of antitrypsin during the following few days and several of these were shown to be antianaphylactic.

It will be recalled that Bronfenbrenner[7, a and c] and Bronfenbrenner and Schlesinger[7b] were of the opinion that many nonspecific agents which raised the antitryptic index of the blood also produced the same resistance to anaphylaxis.

Landsteiner and Chase[43] and Chase[13] reported that "the serum of guinea pigs rendered hypersensitive to certain chemicals, contains antibodies which transfer to the skin of normal guinea pigs reactivity toward the chemical and toward the protein conjugates of incitant." Chase[13] who felt that this principle might have wider applicability, then tested in an analogous manner, serum prepared against proteins. Guinea pigs were repeatedly injected into the skin with horse serum, and positive results were obtained with their sera. Having sensitized sites in normal guinea pigs by the Prausnitz-Küstner transfer method, these sites were reinjected with antigen. In some instances the antigen was injected at a distance from the sites. In both instances the sensitized sites gave early type reactions, with erythema and edema as described for the drug hypersensitivity sera.

Similar effects were seen with guinea pig antiragweed sera. Attempted transfers of human pollen sensitive sera to the guinea pigs were unsuccessful.

Precipitin sera produced in rabbits can be employed for local sensitization of guinea pig skin. The rabbit antisera which were tested, and all of which gave positive skin effects, were: antiovalbumin, "antipicrylovalbumin" (tested against picrylated casein), antipneumococcus III (tested against pneumococcus III polysaccharide). A horse antipneumococcus serum did not show the effect.

No reactions were obtained in the skin of *rabbits* in sites injected with rabbit or guinea pig "immune" serum.

Chase believes the reactions described are due to anaphylactic antibodies. Guinea pigs passively sensitized could be shocked with the homologous antigen, in the case of horse serum and ragweed. Ragweed was not toxic for a normal guinea pig. Much of the foregoing is quoted directly from Chase's paper.

Anaphylaxis in the rabbit may be general or local (Arthus phenomenon). In the dog and guinea pig, antibodies attached to fixed tissue cells seem to be most concerned in the reactions. Anaphylaxis in the rabbit is different, however, and is of considerable interest because analogies are found in human vascular tissue reaction which resemble the Arthus phenomenon.

In the rabbit, the circulating tissue is most concerned in the reaction (Dragstedt, et al.[27]). A large amount of histamine is present in the leucocytes of rabbit's blood and it is assumed that the leucocytes act like the histamine-rich liver of the dog and the histamine-rich lung of the guinea pig. When antigen is added to the blood of a sensitized rabbit, in vitro, there is a shift of histamine from the blood cells to the plasma (Dragstedt, et al.[28] and Katz[42]). The refractory state cannot be accomplished in the rabbit, as in the dog, or guinea pig. There is a leucopenia in all animals, which can be explained by the mechanisms described by Abell and Schenck[1] in the rabbit. It is probable that leucocytic emboli may contribute more or less to the vascular reactions produced by histamine.

The general reaction in the rabbit follows the intravenous shocking dose. In this animal no latent period is necessary between the sensitizing and shocking doses. Cardiac failure is secondary to obstructed flow of blood through the pulmonary circuit. Facts regarding these reactions in the rabbit were discovered by Abell and Schenck in their study of blood vessels in the living ear of the rabbit by means of a transparent moat chamber.

It was noted by direct microscopic observation that arteriolar contraction took place during anaphylactic shock. The following phenomena were also observed: an increased adherence of leucocytes to the walls of these vessels, formation of leucocytic clumps apparently due to increased stickiness of leucocytes toward each other and emigration of leucocytes through the walls of the vessels. No contraction of capillaries or venules was evident, nor was any specific precipitate observed. These effects in the sensitized rabbit could also be demonstrated by direct addition of horse serum-antigen to the moat chamber.

Schenck and Abell[70] believe a similar clumping of leucocytes occurs in man. Concerning the cells which emigrate through the walls, Schenck states: "We are not sure which of these cells are eosinophiles. We are fairly certain most of them are because of the size of the granules in them, but we are still unable to prove it."

The Arthus Phenomenon.—The phenomenon described by Arthus[3] was briefly as follows: Several subcutaneous injections of animal serum

into rabbits changed the local reaction of the skin to subsequent injections of the same kind of serum.

The local reaction progressed in intensity with each injection. Following the seventh, but not necessarily at the seventh injection, the skin underwent central necrosis, and hemorrhage was evident. A morphologic description has been given by Opie.[51, a and b] Nicolle[50] was able to transfer, passively, sensitization to the Arthus phenomenon. Culbertson,[21] quoted by Cannon and Marshall,[11a] "found striking parallelism between precipitin content of serum and the intensity of cutaneous reactivity." He observed also that intravenous injection of a "desensitizing" dose of antigen caused a marked diminution in precipitin content and simultaneous disappearance of cutaneous reactivity. This was *followed* by a concomitant increase in precipitin content and cutaneous reactivity. Removal of precipitins from a serum by antigenic absorption eliminated the capacity of the serum to confer sensitization to a normal animal by passive transfer. The evidence that antibody appears essential for the mechanism of the Arthus phenomenon is convincing.

Using the collodion particle method of precipitation, Cannon and Marshall[11b] showed a definite parallelism between the precipitating potency of the serum and the intensity of cutaneous reactivity, except in young animals. Their correlation table shows the relationship between the precipitative strength of blood serum, and cutaneous reactivity of the Arthus type in 244 determinations in rabbits sensitive to crystalline egg albumen.

HYPERSENSITIVITY IN INFECTIONS

This subject has been recently reviewed by Rich.[59] For the sake of conciseness a number of his fundamental statements will be quoted directly.

"The state of hypersensitivity resulting from contact with bacteria, living or dead, confers on the body ability to react hypersensitively, not only to the protein of bacteria but to bacteria themselves. In contrast, the body that is brought into the state of Arthus hypersensitivity, by repeated injections of protein derived from a given bacterium, will react violently to injections of that protein but will not react hypersensitively to injections of intact bacteria." (Rich;[58] Sabin and Joyner.[66])

"The true sensitizing antigen responsible for bacterial hypersensitivity has not yet been isolated from any bacterium."

THE ROLE OF ANTIBODIES IN THE ARTHUS TYPE OF HYPERSENSITIVITY

Following injection of free foreign protein, bacterial or otherwise, a local or constitutional reaction from subsequent contact develops rapidly and soon reaches its height. This anaphylactic type of sensitivity is transferrable passively, is demonstrable by precipitin test, and uterine

strip contraction, and antibodies are present in the circulation. Rich and Follis[61] and Siebert[75b] have observed the foregoing phenomena in animals sensitized with tuberculin protein.

In contrast, the reaction in bacterial hypersensitiveness is characterized by a slowly developing local or constitutional reaction; there is no smooth muscle contraction and no passive tranference. There are occasional exceptions to these differences. Although no antibodies are demonstrable in this type of hypersensitiveness, Rich believes there are a number of reasons for believing that bacterial hypersensitiveness depends upon specific antibody, which may be present in the cells but not in the circulation. One reason is the high degree of specificity which is difficult to account for except on the basis of antigen-antibody reaction.

Anaphylactic (Arthus type) sensitivity, having been established, will wane gradually if there is no further contact with the antigen. Reintroduction of antigen will then cause the antibody and a state of hypersensitivity to reappear in a shorter time than was required at the first contact (von Pirquet[54]).

This anamnestic response is characteristic also of bacterial hypersensitiveness. Furthermore, bacterial hypersensitiveness can be depressed by suitable desensitization similar to Arthus type desensitization.

In bacterial hypersensitiveness (which may be due to viruses, bacteria, and fungi), there is a general tissue sensitization, while in the anaphylactic type there is a local one.

Vascular reactions in the Arthus phenomenon have been described by Abell and Schenck.[1] Rich and Follis[61] have shown that tissues which contain blood vessels in the Arthus sensitized body are killed by the specific protein, while avascular tissue is not. The Arthus phenomenon cannot be produced in the (avascular) cornea of a sensitized rabbit; but if the cornea of such a rabbit is vascularized it then shows a hemorrhagic reaction on injection with antigen. It appears, therefore, that capillaries are selectively sensitized. It should be mentioned that antibodies penetrate the cornea.

It has been shown[2, 5, 48, 56] that cells of the (anaphylactic) Arthus sensitized body can thrive in vitro in contact with the specific protein. However, when *blood cells or tissue* of a body with bacterial hypersensitiveness are removed and washed, they are killed in vitro by amounts of bacterial protein innocuous to the cells of a normal body under the same conditions.

Rich, Lewis, and Gay[64] studied, in tissue culture, cells from human beings with asthma and hay fever who were extremely sensitive to the specific antigen. Rich[60] states: "We have found that the leucocytes in tissue culture from patients with extreme degrees of hypersensitivity were entirely unharmed by contact of the specific antigen which would have produced extremely severe local reactions in the intact patient. This is quite different from the state of affairs when leucocytes of body with tuberculin type hypersensitivity are brought into

contact with the specific antigen. In the latter case, the cells are killed.''

The mechanism of desensitization in bacterial hypersensitiveness is not understood, but can be accomplished by the usual procedures. Rich is of the opinion that hypersensitiveness is not necessary in protection against infection and may even be harmful, since it intensifies the degree of inflammation and the amount of tissue necrosis. Therefore, while immunity may be present concomitantly with hypersensitiveness, it will function just as effectively in his opinion, if the hypersensitive state is depressed. Schick[68] is not entirely in accord with this theory.

It is of interest to mention that Siebert and Nelson[75b] studied antibody to tuberculin protein, by electrophoretic methods, and concluded that it could be identified in serum as a component with electrophoretic mobility close to α-globulin. It increased in sera following sensitization to protein, and was removed in part with specific precipitate produced by adding antigen to the homologous antiserum. Seibert[75a] emphasizes the fact that this antibody is not important as a defense mechanism against the disease tuberculosis; in fact, it makes guinea pigs more susceptible. Siebert plans to study other antibodies by similar methods.

Rich and Gregory[63] studied cardiac lesions in rabbits subjected to experimental serum sickness. Their observations are highly suggestive that the cardiac lesions of rheumatic fever may be results of hypersensitive reactions of the anaphylactic type. Differences between the ''tuberculin type'' and anaphylactic type of hypersensitiveness have been discussed. The former type was usually considered in relation to rheumatic lesions.

Rich reviews experiments pertinent to his thesis, namely, those of Tillet and Francis:[6] that the pneumococcus gives rise to anaphylactic and tuberculin type hypersensitiveness. The capsular polysaccharide is responsible for anaphylactic hypersensitiveness and the somatic protein is responsible for the tuberculin type. The experiments of Enders[33] showed that the protein is responsible for the tuberculin type hypersensitiveness, but that the infected body may become anaphylactic to the carbohydrate of the bacillus; the experiments of Morris[49] with Friedländer's bacillus were previously mentioned. Coburn,[15] using a nucleoprotein fraction of streptococcus as test material in study of hypersensitive reactions in rheumatic patients, stated, ''immediate wheal and erythema type reactions occurred frequently'' but reactions ''were not reported.''

Although the following experiments belong in the section on anaphylaxis, it seems more pertinent to review them here.

Kopeloff and Kopeloff[42a] in extensive studies of anaphylaxis in *Macacua rhesus* monkeys using horse serum as antigen, and later egg albumen as antigen, observed Arthus type lesions and hemorrhages into the skin. The degree of severity of the necrotic lesions could be correlated with the precipitin titer of the sera.

The gross pathologic lesions are of interest: In fatally shocked animals there were petechial hemorrhages, and larger hemorrhages in the lungs with emphysema; similar lesions in the liver, spleen, pancreas and intestine were also noted. In nonfatal shock there were hemorrhages over the entire body, with edema of the face and conjunctivitis. In one instance there were petechial hemorrhages in both auricles of the heart. There was a reduction in platelets and delayed clotting time. Of seventy-three monkeys used in the second experiment, twenty-one had tuberculosis during one phase of the work. The serologic studies of antibodies are interesting, but space does not permit further review of them. Microscopic studies of tissues were not made.

De Gara and Angevine[24] recently studied reactions in the skin and internal organs of rabbits "sensitized" with streptococcus and pneumococcus vaccine, and the relationship of these reactions to antibodies.

The animals sensitized to the vaccines subsequently received injections of homologous antigen in the liver, spleen, kidney, and anterior stomach wall. There was a higher incidence of reactions in the liver and spleen. Animals passively sensitized with pneumococcus antibody also developed necrotic reactions in the liver and spleen following the injection of homologous antigen into these organs. This effect, in the opinion of the authors, was due to antigen-antibody combination.

Since tuberculin type hypersensitiveness is usually not transferable, passively, and since the serum of animals sensitive and immune to pneumococcus, when transferred passively to normals, confers immunity but not bacterial hypersensitiveness, one might assume that the lesions noted were not tuberculin type lesions. Such serum, however, as demonstrated by Harley,[39] may passively transfer the following: skin "allergy" to SSS (polysaccharide) and NP (nucleoprotein) of pneumococcus; serum antibodies anti-S (virulent), anti-R (avirulent); and type specific immune bodies (anti-SSS).

De Gara and Angevine concluded that there was no relationship between skin reactions and titer of circulating antibody, and no correlation between cutaneous reaction and titer of antibody of extracts of organs. However, they demonstrated that "allergic reactions occur in those organs, namely, liver and spleen, in which antibodies are demonstrable in high titer; and reactions are usually absent in kidney and stomach wall, in which antibody titer is low or negative. It is probable that the reactions are caused by union of antigen and specific antibody in the tissue."

It is of interest that a greater number of lesions occurred in the tissues which were relatively more vascular, that is, liver and spleen. It is possible that some of the lesions observed were of the Arthus type, particularly in the passively sensitized animals.

The experiments of Cannon, Walsh, and Marshall,[12] although they do not belong in the category of hypersensitiveness of infection, are of interest in this connection. They studied the lungs of rabbits sensitized to egg albumen, subsequently given intranasal instillation of a solution

of purified egg albumen. In comparison to neglible pulmonary inflammation in the lungs of the controls, the lungs of the hypersensitive animals showed a pneumonitis, which is described in detail. The authors considered that the primary effect of antigen-antibody reaction in the lungs was an increased capillary permeability, followed later by severer vascular injury; and that the effect was due to an humoral element, presumably anaphylactic antibody, rather than a change in the reaction capacity of the tissue.

Pulmonary reactions in anaphylaxis in rabbits were studied in 1939 by Garipuy[37] who reviewed some of the earlier work including that of Opie.[51, a and b]

Rich and Gregory[62] studied and described rheumatic pneumonitis which appears to have an anaphylactic basis. They state: "The peculiar lesion of rheumatic pneumonitis compared with that of the pneumonitis caused by sulfonamide hypersensitivity, shows that the two are basically identical and they both exhibit a primary capillary damage, characterized by focal anaphylactic reactions." Shaffer, Lentz, and McGuire[69] in a study of sulfathiazole eruptions, found the passive transfer test positive to sulfathiazole. Delayed, positive, tuberculin type reactions as well as early, wheal reactions were reported. The authors believe that pronounced pyogenic sensitivity, especially to the staphylococcus, is important as a predisposing factor in many of the eruptions.

In considering the above findings, it is interesting to speculate as to the exact nature of the pathology of the human lung in the acute stages of pollen type asthma.

A point which seems worthy of note here, also, is that patients suffering from bronchial asthma, with associated upper respiratory infections, namely, tonsillitis, sinusitis, and pharyngitis, are sometimes given sulfonamides. An ensuing pneumonitis might very well be due to sensitivity to sulfonamides, rather than an extension of the upper respiratory inflammation. Such a reaction might be concomitant with pulmonary infection, however.

Bronfenbrenner[9] discusses the relationship of the state of dispersion of bacterial and nonbacterial antigens to the development of sensitization and to the development of antibodies. He believes that anaphylactic and bacterial type hypersensitiveness are basically the same, and that absence of demonstrable antibodies in bacterial hypersensitiveness is not a criterion for the separation of these two forms of hypersensitiveness. They are not, he thinks, necessarily due to a different mechanism. It is interesting that twenty-four hours following a sensitizing injection of egg white into an animal, the skin test with the homologous antigen was negative; on the second to third days, a wheal appeared at the site of the test injection in eight to twenty-four hours; on the fifth to seventh days, an evanescent wheal with erythema appeared. At this latter time circulating antibodies could be demonstrated.

A controversial problem has also been studied by de Gara and Angevine.[23] In this study of the effect of intracutaneous injections of pneumococcus and streptococcus vaccine into rabbits, they observed the presence of antibodies in extracts obtained from the site of injection of antigen into the skin, after an interval of from five to twelve days. The presence of antibodies in lymph nodes before they could be demonstrated in the blood, showed that they were formed at the local site of inflammation. They state: "At the same time, antibodies are formed in organs that fix the antigen, namely spleen, liver, and bone marrow." They mention that antibodies are detectable only when present in a "measurable excess," as suggested by Freund and Opie.[35]

The latter investigators, in 1938, injected rabbits with heat-killed tubercle bacilli and B.C.G., and studied the skin reactions and complement fixing antibodies in the sera. They point out that "it is important to know in what *degree and within what limitations* sensitization or allergic inflammation (in the sense of von Pirquet) increases or decreases resistance against infection. It has long been recognized that resistance to tuberculosis may occur in the absence of sensitization revealed by allergic inflammation."

It is not within the limits of this review to state all of their conclusions, but it should be mentioned that, in so far as the role of antibodies is concerned, "it it probable that the skin test (in tuberculosis) for sensitization, and complement fixation applied to the blood serum measure antibodies or other factors determining sensitization and immunity that are in excess of those actively concerned in the maintenance of resistance."

Shwartzman[74] believes there is a correlation between the phenomenon of local tissue reactivity to bacterial filtrates and some of the characteristic features of bacterial hypersensitiveness. He has demonstrated that bacteria produce, in vitro and in vivo, soluble active principles which elicit a state of nonspecific reactivity in the tissues. These active principles, which he believes are exotoxins, may cause reactions at locally injected areas, following their introduction into the circulation. Nonbacterial and bacterial antigen-antibody complexes injected intravenously may also produce necrotic lesions at locally injected sites. This is an heterologous antigen-antibody complex effect. The local lesions show predominately hemorrhagic and necrotic manifestations. The phenomenon is not considered by Shwartzman to be in the nature of anaphylaxis. No immediate wheal and flare, no sensitizing antibodies, and no passive transference have so far been demonstrated.

It is of interest to mention briefly a few of his experiments. A state of active sensitization to tuberculin having been established by injection of tuberculin into rabbits, the animals were then injected locally with different bacterial active principles. Tuberculin injected intravenously then caused severe hemorrhagic and necrotic lesions in the prepared sites, indicating the effect on these sites of the heterologous antigen-antibody combination. Similar reactions occurred at prepared

sites following intravenous injection of antipneumococcus serum and corresponding "inactive" pneumococcus filtrate.

He believes that "immunity" and "allergy" may represent the same process and states: "The fact whether antigen-antibody complexes are injurious or not may depend on a quantitative relationship between the two, and also on the fact whether or not neutralizing potency is associated with antibodies." It was demonstrated by Shwartzman that when antibodies contain neutralizing potency, antigen-antibody complexes are innocuous.

Experimental studies of neutralizing potency of sera obtained from patients convalescent from meningococcus meningitis, gonococcal infections, and typhoid fever are discussed by Shwartzman. This neutralization is thought to be due to a mechanism different from that mediated by the usual demonstrable antibodies.

Some of the Arthus type reactions reported in man are considered by Shwartzman to be more in the nature of the phenomenon described by him, since many of the cases reported were suffering from acute infectious diseases, in which exotoxins capable of producing the phenomenon were present.

Hypersensitiveness of the Pollen Type in Man

It is hoped that the brief reviews presented thus far, in connection with the newer developments in the fields in anaphylaxis and bacterial hypersensitiveness, may serve to clarify some of the difficult problems encountered in clinical hypersensitiveness.

This part of the review deals chiefly with recent experiments relating to pollen type phenomena.

Hypersensitiveness of the pollen type in man occurs spontaneously and is subject to hereditary influence. Prausnitz and Küstner[55] discovered the transferable (heat labile), skin sensitizing antibodies characteristic of this type of hypersensitiveness, and explained in part the mechanism. Cooke and Spain[20] reviewed the literature on these points. Other developments in this field up to 1935 have been ably reviewed by Gay,[38] therefore, they will be mentioned only so far as they impinge upon a discussion of more recent investigations.

Von Pirquet[54] used the word "allergy" from *ergeia*, reactivity, and *allos*, altered, without being prejudiced as to the bacteriologic, pathologic, or biologic findings. It was a clinical conception and was applicable to accelerated or anamnestic responses of various types; for instance, reaction of the previously vaccinated to subsequent vaccination, and accelerated serum disease in man following a second injection of horse serum.

It should be emphasized, and it has been reiterated by Schick,[68] that "allergy" taken in the original sense of von Pirquet covers not only "hyperergic" reactions but also immunity to infection.

Over a period of four years, Cooke, Barnard, Hebald, and Stull[18] transfused twenty cases of untreated hay fever with the blood of

treated patients, at the beginning of the hay fever season; sixteen of the twenty cases had satisfactory results which lasted through the remaining four or five weeks of the hay fever season. "Ninety-six other patients received repeated 10 c.c. doses of supposedly immune serum, subcutaneously, with clinical improvement in 60 per cent." These results indicated the presence of a transferable protecting substance, which the authors then demonstrated by serologic studies.

They studied the sera of hay fever patients before and after treatment with ragweed pollen antigen, and found evidence of an inhibiting or "blocking" antibody in the sera of the treated cases. They believed that there was a coexistence of sensitization and immunity, and considered the probability that the amount of symptomatic freedom might be proportional to the amount of inhibiting substance found.

Subsequently, Sherman, Hampton and Cooke[71] studied the maternal and cord blood of twelve obstetric cases which had been under treatment for hay fever. The "blocking" antibody, present in the sera of these hay fever patients following treatment with pollen antigen, was also demonstrated in the cord sera. Skin sensitizing antibodies of the mother were not transmitted to the cord blood. Other antibodies studied in these cases were: isoagglutinins and typhoid agglutinins, both of which were present in maternal and cord sera. The authors believe, therefore, that the apparent placental transmission of the "blocking" antibody gives further evidence that it is distinct from the skin sensitizing antibody.

Other studies by Loveless[44] have demonstrated that this antibody resists heating at 56° C. for several hours. Cooke, Loveless, and Stull[19] demonstrated its presence in nonsensitive human beings following the introduction of large doses of ragweed pollen antigen.

Cohen and Nelson[16] demonstrated its unquestionable presence in one of two sheep injected with ragweed pollen. More recently this and other antibodies have been observed in cattle, by Weil and Reddin.[77] Antibodies against pollen antigen have also been observed in rabbits. Briefly they are: precipitins and hemolysins (Sammis[67]); precipitins, complement fixing and skin sensitizing antibodies (Winkenwerder, Eagle, and Arbesman[79]); precipitins and production of local skin reactivity by passive transfer of antiprotein sera (Chase[13]).

The extremely large amount of pollen antigen required to produce these effects in animals, as well as in normal human beings, is in contrast to the amount given to hay fever subjects.

Sammis[67] considered the possibility of a relationship between pollen antigens and blood group substances of human erythrocytes, as a possible cause of constitutional reactions in hay fever subjects, during treatment, but no relationship was demonstrated.

It should be stated that the experiments of Cooke and co-workers have been corroborated by other investigators both here and abroad, but space does not permit a discussion of all of them. References may be found in Cooke's papers.

Sherman[72] studied the sera of thirteen cases of ragweed hay fever during the early months of treatment. He observed their "blocking" antibody response to ragweed Fractions I and II.* The patients had been injected with pollen extract which contained both fractions.

The following observations were made: There was a general decrease in tissue sensitivity (immediate reaction) as measured by direct skin and ophthalmic tests; an increase in skin sensitizing antibodies, at first, and appearance in the serum of the "blocking" antibody which combined with and inactivated one of the principal pollen antigens (Fraction I). In that this antibody is heat-stable, and filterable through the placenta, it resembles other antibodies produced in response to other injected antigens. Sherman states that it may possibly be likened to other univalent soluble antibodies described by Pappenheimer,[25] and Heidelberger, Treffers, and Mayer[40] capable of combining with the homologous antigen in solution, but not forming molecular aggregates of sufficient size to precipitate. Pauling, Campbell, and Pressman[53] state: "It appears that both precipitating antigen and precipitating antibody must be multivalent, at least bivalent."

This report has clinical implications of considerable interest, because for the first time there seems to be some indication as to the cause of constitutional reactions which occur in a certain number of cases during pollen therapy. Sherman is of the opinion that cutaneous tests with the two fractions may be a useful guide in the routine treatment of ragweed hay fever, as the results of this experiment show. The patients were divided into two groups, those showing a reaction to Fraction I only and those showing a re-reaction to both fractions. In spite of difference in dosage, the two groups showed little difference in clinical protection, and little difference in cutaneous and ophthalmic reactions. Those in the second group did show a difference in the development of tolerance for large doses of pollen antigen and in the tendency to constitutional reactions from injections. It was expected that patients in Group II, highly sensitive to Fraction II, and apparently not developing neutralizing antibody to this fraction in the early months of treatment, might show more constitutional reactions and be unable to take large doses. Such was actually the case. The author points out that patients sensitive to Fraction I will also have reactions if dosage is increased too rapidly, but they are less apt to reach a low ceiling dosage, above which they cannot be raised. Sherman states: "These results suggest that the 'blocking' antibody is an important factor in the development of tolerance for pollen extract and that patients are able to take large doses of pollen only if they have formed antibodies that inactivate all of the antigens in the pollen to which they are sensitized."

*Fraction I —Albumin precipitated at pH 4 by 50 per cent saturation with ammonium sulfate.

Fraction II—Precipitated by 100 per cent saturation with ammonium sulfate, after removing Fraction I.

Fraction II gave proteic reaction but had only 1.7 per cent nitrogen.

One should consider the possibility, nevertheless, that there may be other mechanisms of protection following injections of pollen antigen.

The studies of Sherman were extended by Sherman and Hebald.[73] Since the method devised by Cooke of testing patients with dilutions of pollen to determine their degree of sensitivity had limited advantages, it was decided to test a large series of cases with ragweed pollen Fractions I and II, and regular (nonfractionated) extracts. Many of these cases were retested because of a history of constitutional reactions. Tests to regular extracts were found not to be a criterion of the probability of a general reaction. Practically all of the cases who reached a low ceiling dosage, above which they could not be raised, fell into the group most sensitive to Fraction II. They had excellent clinical results with small doses of regular extract. Some patients were treated with Fraction I alone. Some cases sensitive to Fraction II who developed the homologous antibody were able to go above the ceiling dosage of those who did not.

Loveless[44] studied fifty-two ragweed hay fever subjects during three to five seasons. They were treated with nonfractionated ragweed pollen antigen. The number of "intensity hours" of hay fever was compared to the amount of "blocking" antibody in the circulation during the season. A close parallel was observed between antibody-titer and clinical relief in 79 per cent of the cases. The degree of relief, however, correlated with antibody titer, varied among individuals. A titer "which protected some was inadequate for others," and Loveless concluded that hay fever subjects "should be treated according to their particular immunological needs." Pollen counts during the season showed the usual variations.

The accelerated response of the heat-stable "blocking" antibody, induced by introduction of (nonfractionated) ragweed pollen extract, was observed by Loveless.[45] The interval between the primary series of injections and the secondary stimulus was several months. Response to the secondary stimulus seemed to be proportional to the cumulative dosage of the primary series. An antibody ceiling was encountered. Loveless states: "A relatively large primary dosage elicited a better serological and clinical immunity than a small one. Responses to secondary stimuli were also more favorable in a group given a large dose." A few patients taking perennial treatment were observed. They did not show the accelerated response.

Parenthetically, it may be said that perennial treatment for hay fever has become a standard procedure in numerous clinics and is suitable for cases reaching a certain ceiling dosage.

Such treatment produces what appears to be a refractory state. Since tolerance often disappears on cessation of treatment, if the period without treatment be of sufficient length, one must, until further proof is offered, consider the state of decreased pollen sensitivity, in part at least, as one of desensitization. If "immunity" exists one might postulate that such "immunity" would function better if the hyper-

sensitive state was kept depressed. This is in concordance with Rich's theory regarding analogous coexisting states in infectious diseases.

Cohen and Weller[17] studied precipitins against ragweed and grass pollen before and after treatment. Their experiments are in accord with those of Cannon and Marshall.[11a] Using Cannon's collodion particle method of precipitation, they demonstrated precipitins in an untreated case sensitive to glue and fish. In cases treated with ragweed and grass, or both, precipitins against these antigens could be demonstrated with regularity. However, they did not occur regularly in untreated ragweed cases. The authors draw no conclusions as to the significance of precipitins against pollen antigen in man, following treatment. It would be interesting to know whether the anamnestic response of precipitins can be produced.

In Chase's[13] experiments, guinea pigs passively sensitized could be shocked with ragweed antigen. Attempted transfers of human pollen sensitive sera to guinea pigs were unsuccessful. It is not mentioned whether the human sera were taken from treated or untreated cases; the possibility exists that sera of treated cases, regularly containing precipitins, according to Cohen and Weller,[17] might transfer sensitivity to guinea pigs.

Finally, it should be mentioned that Service[68a] studied the properties of polysaccharides isolated from pollens, in relation to anaphylaxis in guinea pigs. The results suggest that polysaccharide may specifically inhibit anaphylactic shock in guinea pigs, sensitized with pollen antigen; it may also inhibit the Dale reaction, when added to the bath.

Maunsell,[47] in a study of cross-desensitization in allergic diseases,* examined the specificity of antiallergic mechanisms. She studied local desensitization of skin: desensitization with one allergen, so there resulted no subsequent reaction to other allergens. The patients showed multiple sensitivities: pollen and fish; feathers and flour. She employed desensitizing injections against two "allergens" (A and B) in each case. She also attempted desensitization with weak skin reacting doses of one allergen, and stronger doses of another.

The results of these experiments were as follows: If desensitization was carried out with two allergens of the same skin activity, reciprocal cross-desensitization occurred. If one allergen was stronger than the other, desensitization was unilateral, and the occurrence of either reciprocal or unilateral desensitization was independent of the biologic group. Desensitization was considered, therefore, to be only a quantitative change and not a qualitative return to a normal response. Observations on histamine reactions in desensitized areas showed that "decrease in allergic reaction is not a mere general refractoriness of tissues, but the result of an antiallergic mechanism." "The fact that cells, desensitized by allergic tests, will still react to a corresponding (?) histamine dose leads to the assumption that, during the process of

*Patients suffering from bronchial asthma, eczema, or hay fever.

desensitization, the liberation of histamine is inhibited or immediately counteracted.''

The author suggests the possibility of altering the reaction of the tissues by introducing the allergen locally; for example, into the nostrils in cases of hay fever.

In the light of the complicated phenomena, characteristic of hypersensitive states in general, it may be safely said that the exact mechanism of protection in hay fever has not as yet been defined. Progress is being made in several laboratories, however.

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Editorial

Approaches to Research

RESEARCH is the essence of science; without it progress comes to a standstill. In young and difficult fields, such as allergy, it becomes absolutely imperative that advancement be made at a regular and increasing rate. Unless this is done, allergy will soon stagnate and become a neglected field of medicine. We must admit that, although we have learned a great deal about allergic phenomena in the last quarter of a century, progress has been slow in comparison with other branches of medicine. The many unknown phases of hypersensitiveness serve as a challenge to those of us who have an interest in its establishment as a more perfected science and specialty of practice. Many improvements are possible for the acceleration of progress in research. At this time, however, we wish to discuss only one aspect of this problem—the necessity for as many individuals as possible to engage in research. This means that many more of us must not only be willing to participate in investigative ventures, but we must be conscious of the problems needed, how they can be approached and what type of assistance may be required.

Many young allergists, and some older ones, not infrequently pose the question "What research work shall I do"? It is true that such a query may denote a lack of broad experience in clinical allergy, an absence of imaginative power, or the realization of an inability to carry out technical procedures. Such qualities, in one degree or another, are, of course, important to the research worker. However, the failure of any person to become research minded is often due to a lack of appreciation of the breadth, scope, and varieties of research and the methods of approaching it.

What are the purposes of research in allergy? These can be divided into relatively few general categories:

1. *The Allergic State.*—This phase of allergy is a challenge and a difficult field of endeavor. The problem can be approached from many angles; they may involve studies of anatomic or physiologic characteristics of allergic persons, or they may entail observations on the endocrine status or the chemistry of the tissues and blood. More extended clinical and experimental investigations on heredity might be pertinent. Many other possibilities exist in studying the mechanism of the constitutional factor.

2. *The Allergic Manifestations.*—Clinical and experimental observation will ultimately uncover new types of allergic syndromes. The

relation between atopy, bacterial allergy, contact allergy, and other types of hypersensitiveness will be the subject of much research for the future. New and improved methods for the recognition of a manifestation as allergic or the differentiation of an allergic individual may be the outgrowth of research.

3. *Specific and Nonspecific Causes.*—Much of the research of the past and the future concerns itself with the specific causes of allergy. As time passes new groups of causes of allergic disease are uncovered. In the last ten or fifteen years, such specific agents as insect emanations, fungi, aminopyrine (agranulocytosis), sulfonamide derivatives, and simple chemical substances have been incriminated and have been added to our list of etiological factors. Much remains to be done along less conventional channels, such as a more extended series of studies of sources of simple chemical substances in the food and in the air, and more concerted studies of bacterial allergies and intrinsic agents. There are still too many instances of atopy and other allergy for which no specific cause is as yet known. The mechanism of the action of the antigen needs greater attention. The effect and mechanism of physical factors, such as cold, heat, barometric pressure, humidity and electrical charge, and the effect of climate deserve more orderly and intensive study. The influences of the state of the nervous system, infection, and many other nonspecific phases of allergy require greater elaboration.

4. *The Diagnosis.*—Much still remains to improve diagnostic efficiency and accuracy in allergy. Perfection and standardization of antigens, and the discovery of new types of antigens have already been mentioned. Research dealing with a better understanding of the various types of allergic diagnostic reactions will do much to improve the science of allergy. Finer and more accurate methods for the diagnosis of early complications and more certain measures for the differentiation of allergic from nonallergic manifestations are among some of the needed researches.

5. *Treatment.*—Boundless opportunity exists in the field of therapy. Many investigations are being carried on at present in the attempt to discover new and improved palliative remedies. In a large part, these and future investigations aim to accomplish one or more of the following effects: substitution therapy, in case of tolerance, etc.; more potent action; more lasting effect; and minimization of undesirable reactions. Specific treatment is still in its infancy. The usual effect of partial, temporary, and uncertain protection from desensitization is a challenge to embark on research of various types aiming to explain the inconstancies and to devise improvements to correct them. The mechanism of desensitization, and the immunity processes concerned, should engage the attention of more workers than it has up to the present. And, finally, not to be neglected is a more intensive study of the methods and mechanisms of nonspecific factors and remedies on the allergic state.

METHODS IN RESEARCH

Let us now examine by what general approaches and methods such investigations can be carried out.

1. *Reviews.*—Collecting and bringing together the published reports on some phase of allergy is a legitimate form of research, particularly if such a review is exhaustive and critical. In this way, some papers that would ordinarily escape the average reader are made generally available. In this group may also be included historical accounts. All of these require research into the literature. It should be added, however, that many reviews distinctly lack any of these qualities, being in effect merely an array of abstracts of papers readily available.

2. *Clinical.*—It is in the strictly clinical field that the average practitioner is apt to make new observations. The opportunities in this field are many. New manifestations of allergy are still to be found. The effect of certain recommended therapies on clinical results (vitamin C, histamine, variable schemes in specific treatment, palliative remedies, etc.) offers a wide range for clinical observation in which the experienced clinician should be able to excel. In the same category may be placed diagnostic reports: for example, the incidence of reactions to fungi in the particular worker's territory; the incidence of emphysema; the incidence of other complications; and the effect of weather, climate, diet, nervous factors, etc., on a series of allergic patients. Case reports having to do with an unusual manifestation, cause, complication or effect of treatment may add to our store of knowledge. Many facts systematically obtained in history taking, if summarized and analyzed, may constitute worth-while clinical research.

3. *Physiologic.*—Much of the clinical observation can be made more valuable and more exact by physiologic studies. For example, the therapeutic effect of nasal decongestants by volumetric studies of the air flow enhances the scientific accuracy of such a therapeutic appraisal. The effect of symptomatic remedies on the blood pressure, pulse rate, circulation time, vital capacity, and physical activity are examples of physiologic observation. Such and similar observations in the course of allergic manifestations, as a result of complications or in the presence of secondary factors, are worthy of study.

4. *Pathology, Microscopy, Bacteriology, and Biology.*—One who has experience in pathology or access to such aid can make contributions from gross and microscopic autopsy specimens, from human biopsies and from animals subjected to a variety of experimental studies in hypersensitiveness. Observation of the formed blood elements, such as eosinophils and thrombocytes, under various conditions and technical variations, is another outlet. Microscopic study of secretions and excretions, such as nasal, bronchial, intestinal, and vaginal, still require amplification. Pollen and spore counts with the old and new volumetric methods offer ample opportunity for useful research in many

localities. Botanic and zoological investigations can aid us in our basic knowledge of allergy. Bacterial studies of air and excretions in their possible correlation with allergy should not be totally neglected. The relation of bacterial disease to hypersensitive phenomena is in itself a tremendous field for future experimentation.

5. *Chemistry of the Body.*—Thus far no decided changes in the chemical constituents of the body have been shown to occur as a result of the allergic state, symptoms, or therapy. However, such studies should not be ignored. These may comprise the quantitative determination of inorganic blood constituents (K, Na, P, Cl, Ca, etc.) or the organic chemistry, or the vitamin content, enzyme content, or the endocrine assay, acid-base balance, hydrochloric acid in gastric contents, and more complex chemistry of the secretions and excretions. The main requirement for research along these lines is some knowledge of physiologic chemistry and ability or assistance in carrying out the technical chemical procedures.

6. *Direct Skin Test and Other Tissue Responses.*—By the direct skin tests, a great deal of investigation can be accomplished. New specific causes of atopy and other allergy can be demonstrated, the atopic nature of an antigen can be surmised and antigenic relationship can be observed between various antigens. By quantitative skin reactions the potency of antigens can be studied with relation to various methods of preparation, stability, and sources of the crude material. Similar technical methods can throw light on the behavior of the patient with regard to the effect of desensitization and variations in reactivity due to physiologic and pathologic changes and drugs. Mucous membrane and other tissue reactions can also be used for some of these problems.

7. *Immunological Studies in Man.*—The clinician is inclined to steer shy of immunologic techniques because of a preconceived notion of their difficulty. This is true of some procedures, but on the other hand many are relatively simple and all can be mastered by most people. The reagin transfer technique lends itself to many research studies, such as the determination of the immunologic and atopic nature of an antigen; the relationship of antigens (by cross-desensitization); degree of absorption of antigens; the effect of drugs, physiologic states and modification of the antigen on absorption; and the titer of reagin and the conditions modifying it. Studies on the blocking or protective antibody, although more difficult, are not outside the capabilities of many. Such researches may be used to investigate the mechanism of clinical protection; the effect of various methods and techniques of specific desensitization on the titer of antibody; the influence of acute infections, x-ray and nonspecific therapy on the immune state, and the relationship between circulating and sessile antibodies. A number of other immunologic studies in man (heterophile antibodies, complement, induced sensitivity, etc.) may require different procedures.

8. *Immunologic Studies in Animals.*—A host of investigational projects can be approached by means of the anaphylactic reaction in laboratory animals. By this method one can study the antigenicity of a substance, its crossed relationship to other antigens, the effect of the modification of the antigen on its antigenic power, and the antigenic behavior of haptens, drugs, and simple chemical substances. One can also determine the effect of various conditions, drugs, diet, endocrines, and other metabolic changes on the anaphylactic state. Intestinal and uterine horn contraction (Schultz-Dale technique) of the sensitized guinea pig can be employed for similar purposes as the anaphylactic reaction, and lends itself even better to the pursuit of many problems in hypersensitiveness. The chemical and physiologic changes accompanying the anaphylactic state may throw light on the mechanism of allergy in man. Among other methods of immunologic studies in animals are skin reactions, precipitin and agglutinin studies, and the effects of serum sickness. The Arthus and Shwartzman phenomena deserve greater consideration as an experimental outlet for problems in hypersensitiveness. Animals can also be used for allergy studies to determine absorption of antigens in various forms and to test the pharmacologic action of drugs.

9. *Antigens.*—Chemical study of antigens will help materially to solve some of the riddles of allergy. Purification of antigens, fractionation, and conjugation of haptens are all requisite steps in the preparation of special antigens for immunologic and other studies. For these and other technical procedures, such as electrophoretic separation of antigens, special experience or assistance is, of course, required. Future progress in allergy depends to a large extent on the participation of anatomists, physiologists, chemists, physicists, botanists, biologists, immunologists, eugenists, and even mathematicians. But it depends even more on the clinician, who is not only able to accomplish some of the simpler researches but is farsighted enough to enlist the aid of other scientists and practitioners in other fields of medicine, such as pediatricians, rhinologists, dermatologists, psychiatrists, and others.

Although the above outline lacks much detail and is not intended to be complete, its purpose is to show that research in allergy is not fortuitous but possesses an orderly system in its objectives and the methods to implement it. It is hoped that deliberation along such channels will aid in stimulating more individuals to participate in projects which will advance the field of allergy.

—*S. M. F.*

Annual Meeting

THE AMERICAN ACADEMY OF ALLERGY

At the first Annual Meeting, to be held at the Waldorf Astoria Hotel in New York on December 11 and 12, the following guest speakers will participate.

DR. DAVID PRESWICK BARR

Dr. David Preswick Barr is Professor of Medicine at Cornell University Medical School and Physician in Chief to the New York Hospital. His subject will be "Allergy in Relationship to Internal Medicine."

Dr. Barr is President-elect of the American College of Physicians, past President of the Association for the Study of Internal Secretions; a member of the American Board of Internal Medicine, and of the Committee on Gas Casualties, National Research Council. He is on the editorial board of several scientific journals and is the editor of *Modern Medical Therapy in General Practice.* His researches on muscular exercise, fever, and calcium metabolism are well known.

Dr. Paul Roberts Cannon

Dr. Paul Roberts Cannon, Professor of Pathology and Chairman of the Department at the University of Chicago, will speak on the "Nutritional Aspects of Globulin Metabolism." His recent investigations in that field are outstanding.

Dr. Cannon's interests in the past have included cellular and tissue immunity with especial study of the Arthus phenomenon, intestinal and respiratory infections, experimental malaria, studies on the spleen

and anemia; allergy and chemotherapy. He is associate Editor of the *Journal of Immunology* and of the *American Journal of Pathology;* past president of the American Society of Pathologists and Bacteriologists, of the Association of Immunologists, and of the Chicago Pathological Society. He is a member of the committee on pathology, National Research Council, of the National Influenza Commission, and of the American Board of Pathology.

DR. HANS SELYE

Dr. Hans Selye, Associate Professor of Histology, McGill University, will speak on "Diseases of Adaptation." Dr. Selye has had extensive training abroad and is a member of many distinguished scientific societies, here and in Europe. He is past president of the Montreal Physiological Society.

Dr. Selye is well known for his conception of the "alarm reaction." His work on the physiology of pregnancy and lactation and his more recent work on the pharmacology of steroid hormones, and of adrenal function, particularly in relation to periarteritis nodosa, is of outstanding distinction.

Dr. Carl Albert Dragstedt is Professor of Pharmacology at Northwestern University Medical School, and an authority on the significance of "Histamine in Anaphylaxis," which is the title of his lecture. His experimental work on this phase of allergy is classic.

DR. CARL ALBERT DRAGSTEDT

Dr. Dragstedt, long a member of the revision committee of the U. S. Pharmacopœia, has widespread interests in the fields of pharmacology, biochemistry, and immunity, as testified by his publications on such subjects as epinephrine, diuretics, cocaine poisoning, intestinal infection, physiology of bone, parathyroid secretion, anemia, and anaphylaxis.

Dr. Eugene Markley Landis, Professor of Physiology at Harvard Medical School, will speak on "Factors Influencing Capillary Permeability." Dr. Landis, past president of the American Society for Clinical Investigation, secretary of the Committee on Aviation, National Research Council, recently Professor of Medicine at the University of Virginia, has been the recipient of many awards. His interest in circulatory phenomena is reflected in his distinguished experimental work on the pathogenesis of edema, peripheral vascular disorders, and his recent contributions and critical evaluation on the relationship of renal participation in the production of vascular hypertension.

Members who will participate in the program are reminded that their contributions must be submitted to the JOURNAL OF ALLERGY for publication, subject to approval of the Editorial Board. In order to have the proceedings of the meeting appear in the March issue, it is necessary that contributors hand in their completed manuscripts at the meeting.

Notes

The Committee on Education announces that it is compiling a roster of names of physicians who are seeking residencies in allergy. Applications may be addressed to Dr. Robert A. Cooke. Plans are progressing for the development of facilities for graduate and postgraduate training.

Word has been received of the death of Dr. Rudolf Hecht, who was killed in France, September 16. A further appropriate notice will be published.

Friends of Dr. Charles A. Spivake, formerly a member of the American Association for the Study of Allergy, have forwarded an announcement of his death. They emphasized his devotion to that society, his contributions to the field of allergy and his personality, which makes him acutely remembered.

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